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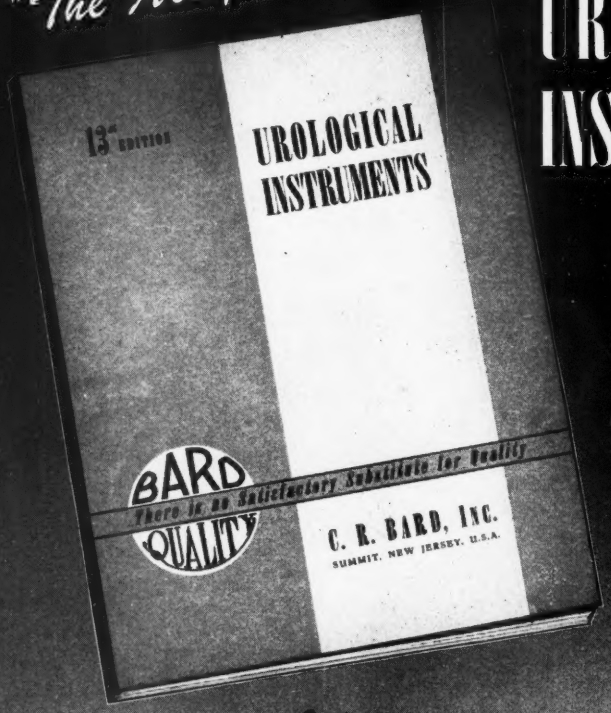


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VOLUME 94 JUNE, 1952 NUMBER 6

# A NOTE ON ESTIMATES OF THE RATE OF DEVELOPMENT OF METASTASIS IN PATIENTS WITH CANCER OF THE BREAST

ALEXANDER G. GILLIAM, M.D., Bethesda, Maryland

IN a recent consideration of "The Absolute Curability of Cancer of the Breast," Park and Lees present data showing the percentages of patients in whom axillary metastasis was demonstrated at operations performed in successive intervals following onset of symptoms.[1] These data, taken from Table II of that article, are given here in Table I. It is observed that axillary metastasis was demonstrated in 60 per cent of those examined in the first month of symptoms. In intervals subsequent to 1 month this proportion, with some irregularities, gradually increased and was 75 per cent in those examined 12 months after onset. The numbers of patients available in individual later intervals are small, but the average for those examined from 13 to 60+ months after onset is also 75 per cent.

Park and Lees formalize these data in a regression equation which is plotted in Figure 1. They conclude from this that: "(a) About 60 per cent of patients with diagnosed cancer of the breast have microscopically detectable axillary metastases at the time of onset of symptoms. (b) There is an increase in the incidence of such metastases with increased duration of the tumor after onset of symptoms. This increase is of the order of 12 to 15 per cent over the first 3 years. (c) About 20 to 30 per cent of patients with diagnosed cancer of the breast do not develop axillary metastases within 3 years of onset of symptoms."

It is the purpose of this note to raise questions concerning the validity of these conclusions and to present alternative estimates of the rate of development of metastasis in this series of patients.

If this group represented cases discovered through routine physical examination, it would be entirely proper to assume that increases in the percentage with metastasis in succeeding intervals from onset actually reflected progression of disease. This, however, is not so. As a group, these patients sought care for illness and, if the presenting symptoms were similar to those in the series of Haagensen and Stout, the illness was related to abnormal signs in the breast. Under these conditions and in view of the well known clinical progression of cancer of the breast, it is entirely reasonable to believe that a group of patients with metastasis is more likely to have signs and symptoms which will induce them to seek care than would exist in a group without metastasis.

Implicit in the significance attached by Park and Lees to their regression equation is

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[1]The well known difficulty of arriving at a reliable estimate of the onset of symptoms is unimportant to Park and Lees' argument, or to that followed here.

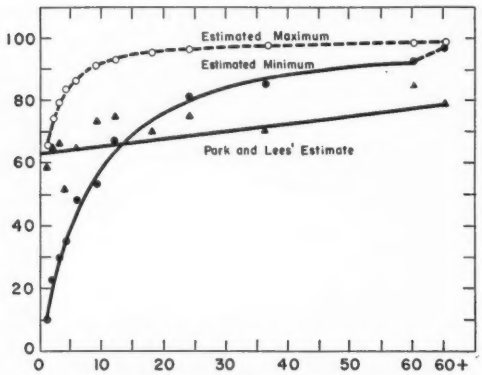


Fig. 1. Three estimates of the percentage of patients with axillary metastasis in successive intervals after onset of symptoms. (For the assumptions on which estimates are based, see text.) Abscissa indicates number of months after onset of symptoms; ordinate indicates percentage of patients with axillary metastasis.

the assumption, that in respect of metastasis, their patients entered observation at random. This assumption would be valid only if the concomitants of progression of disease, as implied by the existence of metastasis, were in no way related to the patients' appearance for diagnosis and treatment. This hardly seems realistic. A more reasonable assumption would appear to be that the symptoms and signs generally found in a group of patients with metastasis are of the kind which induce women to seek medical care for their disease. Under this assumption, Park and Lees' data do not measure the increment of metastasis in intervals following onset but merely indicate that in from 60 to 75 per cent of patients metastasis is in fact intimately associated with the clinical factors which induce women to seek medical aid.

It is unfortunately not possible to measure directly the increment of metastasis through analysis of clinical material of this kind. The percentage actually observed with metastasis in the first month refers only to those patients examined in that month. It is thus unlikely to represent the true percentage with metastasis then since it leaves out of consideration the bulk of patients in a series who also pass through this interval but do not come in for examination until later. The true status of the latter patients is of course unknown until the time they are actually examined. Any estimate made of their status in the first month, from data such as these, therefore involves assumptions.[1] The assumption implicit in Park and Lees' estimate is hardly consistent with what is known of the general clinical progression of disease in patients with cancer of the breast.

TABLE I.—BREAST CANCER PATIENTS DEMONSTRATING AXILLARY METASTASIS AT OPERATIONS PERFORMED IN SEVERAL MONTHLY INTERVALS FOLLOWING ONSET OF SYMPTOMS*

| Duration of symptoms, months | No. of patients with metastasis | No. of patients without metastasis | Total No. examined in interval | Per cent with demonstrated metastasis |
|---|---|---|---|---|
| 0– 1 | 88 | 61 | 149 | 59.1± 4.0 |
| – 2 | 89 | 47 | 136 | 65.4± 4.1 |
| – 3 | 61 | 31 | 92 | 66.3± 4.9 |
| – 4 | 24 | 22 | 46 | 52.2± 7.4 |
| – 6 | 80 | 44 | 124 | 64.5± 4.3 |
| – 9 | 28 | 10 | 38 | 73.7± 7.1 |
| 12 | 72 | 24 | 96 | 75.0± 4.4 |
| 13–18 | 20 | 8 | 28 | 71.4± 8.5 |
| 19–24 | 37 | 12 | 49 | 75.5± 6.1 |
| 25–36 | 12 | 5 | 17 | 70.6±11.1 |
| 37–60 | 17 | 3 | 20 | 85.0± 8.0 |
| 60+ | 14 | 5 | 19 | 73.7±10.1 |
| Total | 542 | 272 | 814 | 66.6± 5.2 |

*Data from Park and Lees (6), Table II.

A *minimum* increment of metastasis in intervals following onset may be estimated from these data on the assumption that patients observed with metastasis in any interval actually developed it in that interval. Under this assumption, for example, the 72 patients out of 96 examined between the tenth and thirteenth month after onset (Table I) did not have metastasis at the end of the ninth month but developed it in the interval in which they were examined. Computations of the true rate of metastasis in all 814 patients in this series, *on the basis of this assumption*, are given in Table II and the data are plotted in Figure 1. Under this assumption, the minimum possible proportion with metastasis in

[1]The same considerations applied here to Park and Lees' discussion of metastasis in relation to duration of symptoms are also applicable to their analysis of data with regard to size of tumor and metastasis.

TABLE II.—CALCULATION OF MINIMUM PERCENTAGE[1] OF ALL 814 CASES WITH METASTASIS IN EACH INTERVAL AFTER ONSET OF SYMPTOMS

| Duration (onset of symptoms to examination), months | No. of patients with symptoms, but not examined, at beginning of interval | No. of patients examined in each interval | | Proportion developing metastasis during interval[1] | Proportion without metastasis during interval[1] | Percentage of original 814 cases without metastases at end of interval | Percentage of original 814 cases with metastases at end of interval |
|---|---|---|---|---|---|---|---|
| | | With metastases | Without metastases | | | | |
| (x) | ($l_x$) | ($w_{x1}$) | ($w_{x2}$) | (p) | (q) | ($100q_x \cdot q_{x+1}$) | [$100(1-q_x \cdot q_{x+1})$] |
| 0– 1 | 814 | 88 | 61 | .1081 | .8919 | 89.19 | 10.81 |
| – 2 | 665 | 89 | 47 | .1438 | .8562 | 76.36 | 23.64 |
| – 3 | 529 | 61 | 31 | .1153 | .8847 | 67.56 | 32.44 |
| – 4 | 437 | 24 | 22 | .0549 | .9451 | 63.85 | 36.15 |
| – 6 | 391 | 80 | 44 | .2046 | .7954 | 50.79 | 49.21 |
| – 9 | 267 | 28 | 10 | .1049 | .8951 | 45.46 | 54.54 |
| 12 | 229 | 72 | 24 | .3144 | .6856 | 31.17 | 68.83 |
| 13–18 | 133 | 20 | 8 | .1504 | .8496 | 26.48 | 73.52 |
| 19–24 | 105 | 37 | 12 | .3524 | .6476 | 17.15 | 82.85 |
| 25–36 | 56 | 12 | 5 | .2143 | .7857 | 13.47 | 86.53 |
| 37–60 | 39 | 17 | 3 | .4358 | .5642 | 7.60 | 93.40 |
| 60+ | 19 | 14 | 5 | .7368 | .2632 | 2.00 | 98.00 |
| Total | (814) | 542 | 272 | | | | |

[1]Minimum percentage with metastasis is that occurring on the assumption that those with metastasis developed it during period in which they were examined, and hence were free of metastasis prior to that period. Computation also assumes that those without metastasis subsequently developed it at same rate as those in whom it was demonstrated.

the first month after onset is only 11 per cent, or 88 out of all 814 patients, rather than the 60 per cent estimate of Park and Lees.

The *maximum* possible increment of metastasis may be computed on the assumptions, (a) that all 542 patients in whom it was observed actually developed it in the first month, and (b) that the remainder were not treated, remained under observation, and developed metastasis in the interval following that in which no metastasis was demonstrated. These computations are not shown but the results are also plotted in Figure 1.

It appears likely that the *true* increment of metastasis, in intervals following onset of symptoms, lies somewhere between the maxima and minima[1] plotted in Figure 1. Examination of this figure shows that the maximum estimate corresponds to Park and Lees' estimate only in the interval of less than 1 month after onset of symptoms. The minimum approximates their estimate at the twelfth month.

The assumptions on which the minimum proportions are computed would appear to be reasonable when the intervals are of 3 or more months' duration; that is between onset and 3 months, and for the plotted intervals thereafter. They appear particularly appropriate since such a large proportion of patients are observed to have metastasis when they finally appear for definitive treatment. If this is correct, then, about 30 per cent[2] of the tumors in this series metastasized rapidly. This figure, however, is dependent upon the validity of the stated assumptions, and an appropriate means of testing these assumptions is desirable. It appears, nevertheless, to be more realistic than Park and Lees' estimate of 60 per cent.

The vital general questions raised by Park and Lees and, previously, on the basis of dif-

[1]The estimated minimum does not cover the possibility that a larger proportion of the 272 patients might *never* have developed metastasis. In this case the minimum given in Figure 1 is too high for the later intervals since it assumes that the 272 patients would have developed metastasis at the same rate as calculated for those in whom it was observed.

[2]Two hundred thirty-eight (63.1 per cent) of the 377 patients presenting themselves for treatment in the first 3 months had demonstrable metastasis, but these 238 are only 29.2 per cent of all 814 who might have been diagnosed during that interval if they had had compelling clinical or other reasons for seeking medical care. The contention here is that the clinical progression of disease, which is generally associated with metastasis, provided the compelling reason in from 60 to 75 per cent of the patients.

ferent kinds of evidence, by McKinnon(3,4,5), and by MacDonald, resolve themselves into the critical basic question of the true proportion of rapidly growing or metastasizing tumors in any representative series of cases of cancer of the breast. The fact that such tumors exist is evident in any clinical series. It is also obvious that there will be fewer of them in a large group of patients without metastasis than could exist in a group with metastasis. It must be emphasized, however, that their true proportion cannot be measured directly from data of this kind. Any proportion arrived at is an estimate at best, and as such involves assumptions. As a consequence, the merit of any estimate is directly dependent upon the general validity of the assumptions made.

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# CANCER OF THE BREAST

## Analysis of Frequency, Distribution, and Mortality at the University of California Hospital, 1918 to 1947, Inclusive

MICHAEL B. SHIMKIN, M.D., ESCHECHOLTZIA L. LUCIA, Ph.D., ROBERT S. STONE, M.D., and H. GLENN BELL, M.D., F.A.C.S., San Francisco, California

CANCER of the breast in women in the United States has the highest prevalence rate of any form of neoplastic disease in either sex (7). It has been stated (16) that more articles have appeared on the subject of cancer of the breast than any other single regional form of cancer.

The general acceptance in the major clinical centers of the radical dissection of the breast devised by Halsted and by Willy Meyer has led to a systemization of the surgical treatment of mammary cancer for the past half century. The limitations of the operations were recognized with experience, leading to a clearer delineation of the operable and nonoperable cases (12). This resulted in more rigorous selection of cases considered eligible for the radical mastectomy, and a consequent improvement in 5 year survival rates among patients undergoing the operation.

The role of radiation in the treatment of carcinoma of the breast is a controversial topic. Some improvement in the 5 year survival rates has been claimed through the use of postoperative x-ray therapy, particularly when such therapy has been given in doses above 2,000 roentgens to patients with axillary lymph node involvement (15). The general opinion in most clinical centers in the United States is expressed by Haagensen, that "critical evaluation of the evidence at hand does not give radiation any substantial place in the curative attack on carcinoma of the breast. Although it is widely used as a supplement to surgery, its value has not been proved."

From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, Public Health Service, Federal Security Agency and the Division of Medicine, Cancer Research Institute, Division of Radiology, Division of Surgery, University of California School of Medicine, San Francisco, California.

Comparisons of survival in cancer of the breast, particularly when such comparisons are attempted between different centers, encounter a number of difficulties. The lack of a commonly accepted method of clinical staging of the disease, such as is available for carcinoma of the uterine cervix, precludes determinations of the distribution of the populations in respect to the extent of the disease. The results of treatment usually relate to a particular type of treatment, with the degree of selection of individual cases and the criteria of such selection not being given. The methods of presenting the data vary widely, particularly in regard to untraced cases, and the analyses seldom include determinations of statistical variance and tests for statistical significance of differences.

In order to provide a base-line for subsequent studies and comparisons, a review[1] was made of the incidence, distribution, and mortality among female patients with primary carcinoma of the breast recorded at the University of California Hospital and Clinics during the 30 year period 1918 to 1947, inclusive. Emphasis was placed upon the statistical analysis of three interrelated topics: (a) examination of the *total* data for homogeneity, in order to ascertain whether cases observed during earlier years are similar to cases observed during more recent years, (b) examina-

[1]The results reported here are the work of the surgical staff of the University Hospital, represented during the past 30 years primarily by W. I. Terry, E. I. Bartlett, H. G. Bell, H. H. Searls, L. Goldman, and H. J. McCorkle, and of the radiotherapists, primarily R. S. Stone and B. V. A. Low-Beer. The follow-up of the cases is essentially the devoted work of Elinor F. Wells. We have been assisted by the staffs of the Record Room, under Martha A. Buck, and of the General Tumor Registry, particularly Helen Ferris and Katherine C. Oppermann.

Portions of the data analyzed in this study have been published previously from somewhat different viewpoints by Bartlett and by Bell.

TABLE I.—DISTRIBUTION OF CASES BY STAGES OF THE DISEASE AND BY CHRONOLOGIC PERIODS

| Period years | Stage of disease at admission* | | | | Total No. |
|---|---|---|---|---|---|
| | I No. | II No. | III No. | IV No. | |
| 1918–1924 | 26 (1) | 42 (1) | 24 (2) | 2 (0) | 94 (4) |
| 1925–1929 | 46 (1) | 36 (2) | 27 (0) | 16 (1) | 125 (4) |
| 1930–1934 | 33 (4) | 34 (0) | 46 (1) | 23 (2) | 136 (7) |
| 1935–1939 | 56 (2) | 61 (1) | 75 (0) | 33 (1) | 225 (4) |
| 1940–1944 | 119 (6) | 97 (6) | 78 (4) | 25 (0) | 319 (16) |
| 1945–1947 | 54 (2) | 29 (0) | 64 (7) | 10 (0) | 157 (9) |
| Total | 334 (16) | 299 (10) | 314 (14) | 109 (4) | 1056 (44) |

*Numbers in parentheses are bilateral cases (44 patients)

tion of data relative to age and delay, and the relationship of these factors to survival, and (c) examination of survival at yearly periods by stage of the disease and by type of treatment.

## MATERIALS AND DEFINITIONS

All records on all patients with cancer of the breast *recorded* at the University of California Hospital and Clinics during the years 1918 to 1947, inclusive, were personally examined. The data from the records, including follow-up, were transcribed on punch-cards.

The records of 1,056 female patients with primary carcinoma of the breast were used for analysis. Patients with other neoplastic disease of the breast, such as sarcoma, were not included. Male patients were not included. Some 264 women with recurrent carcinoma of the breast were excluded. The following groups, comprising 95 patients, were also excluded from consideration: 45 patients on a "come and go" status, who had no unit records or other information at the hospital; 45 patients who were treated elsewhere and were merely followed at later periods at the hospital; and 5 patients who had one visit, without biopsy or treatment, who were referred elsewhere for medical care.

The material, as summarized in Table I, was analyzed on the basis of the following definitions.

1. *Diagnosis.* Positive pathologic diagnosis of carcinoma of the breast, based on biopsy of the primary lesion or a metastasis, was the chief criterion of diagnosis. Of 1,056 cases, 992 had such evidence during the course of the illness, a 94 per cent pathologic verification. As given in Table II, 64 cases were accepted without pathologic proof. This was done on the basis of unequivocal clinical and/or roentgenographic evidence; all but 2 of these patients had advanced, metastatic disease.

2. *Age at onset, delay, and treatment.* The date of the first sign or symptom attributable to subsequently established carcinoma of the breast, noted by the patient or a physician, was taken as the apparent time of onset. The age at that time was equal to the age at admission less the delay period, and was recorded in 1,038 of the 1,056 cases. The delay period was recorded separately in months as units. In patients with bilateral carcinoma, the involvement of the first breast was used for the determination of the age at onset and delay. The age at admission to the hospital or clinic coincides in almost all cases with the age at treatment. In determining survival after treatment, the period in months after operation was used for all patients who underwent surgical removal of the breast. In patients

TABLE II.—PATHOLOGY AND LOCATION OF LESION

| Stage | Total No. | Pathology No. of cases | | Side of lesion* No. of cases | | | Location of lesion No. of cases | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Verified | Not verified | Right | Left | Unknown | Outer quadrants | Inner quadrants | Nipple area | Unknown |
| I | 334 | 333 | 1 | 171 | 163 | — | 199 | 95 | 15 | 25 |
| II | 299 | 298 | 1 | 151 | 148 | — | 188 | 68 | 20 | 23 |
| III | 314 | 300 | 14 | 135 | 178 | 1 | 168 | 61 | 25 | 60 |
| IV | 109 | 61 | 48 | 52 | 55 | 2 | 41 | 12 | 2 | 54 |
| Total | 1056 | 992 | 64 | 509 | 544 | 3 | 596 | 236 | 62 | 162 |

*Bilateral cases were tabulated in respect to first tumor noted.

with advanced disease treated with x-ray therapy alone, or those receiving palliation or no treatment, survival was calculated from the date of first admission for the breast condition.

3. *Stage of disease.* The records were evaluated by one medical examiner. On the basis of available clinical and pathology evidence recorded at the time of diagnosis and presented in the unit record, the cases were classified into four stages according to the criteria proposed by Portmann. Stage I represents cases with cancer localized to the breast, without involvement of the skin or lymph nodes, or attachment to deeper structures. Stage II includes similar cases, but with some axillary lymph node involvement. Stage III includes cases with skin involvement, satellite tumors, fixed tumors, and extensive axillary lymph node involvement. Stage IV consists of cases with evidence of distant metastases.

Bilateral carcinomas of the breast were included in the staging, but considered as single patient entities for purposes of analysis. For example, a patient with stage I disease who subsequently developed stage II carcinoma of the other breast was retained in the stage I group. Patients with simultaneous bilateral mammary cancer were placed in stage III, or in stage IV if distant metastases were present.

4. *Surgery.* All patients designated as having had a radical mastectomy had the full Halsted operation. There were removed in one block at least 8 centimeters of skin from the palpable edges of the tumor, the pectoralis major and minor muscles, all axillary fat, loose areolar tissue, lymph nodes, and branches of the axillary vein. Any procedure less than this was considered a simple mastectomy, whether with or without partial axillary dissection.

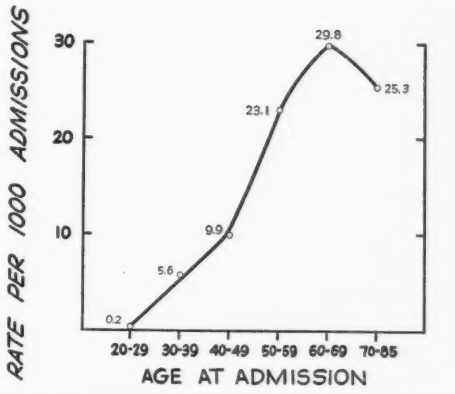


Fig. 1. Frequency of females with cancer of the breast per 1,000 female admissions to the University of California Hospital 1918 to 1947, inclusive. The overall frequency rate is 11.9 per 1,000.

5. *Radiation treatment.* Patients were designated as having received x-ray treatment before or after surgery if at least 3 fields, the breast, axilla, and supraclavicular areas, were treated during 3 to 6 weeks for a total dose per field of 1,800 roentgens in air, or a tissue dose of at least 2,000 roentgens. The same definitions of dose, time, and ports were used for cases in whom x-ray was the primary or the only treatment. Roentgen treatment for recurrence, metastases, or in doses less than the above was not considered as constituting preoperative or postoperative radiation therapy.

6. *Follow-up.* The cases were followed to January 1, 1950. At that date, as given in

TABLE III.—STATUS AND FOLLOW-UP OF THE CASES OF CANCER OF THE BREAST, 1918–1947

| Stage | Total No. | Known dead, No. of cases | | | | | | | Known alive at latest follow-up, No. of cases | | | | Lost before 5 years, No. of cases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cancer present | Cancer absent | Unknown | Post-operative | Total dead | Autopsy performed | Cancer other than breast* | Jan. 1, 1950 | At 5 years | At 10 years | Total | |
| I | 334 | 90 | 49 | 14 | 3 | 156 | 13 | 16 | 142 | 12 | 17 | 171 | 7 |
| II | 299 | 166 | 29 | 17 | 3 | 215 | 23 | 4 | 67 | 6 | 9 | 82 | 2 |
| III | 314 | 240 | 19 | 16 | 1 | 276 | 20 | 6 | 28 | 2 | 3 | 33 | 5 |
| IV | 109 | 98 | — | 8 | — | 106 | 14 | 2 | 1 | — | — | 1 | 2 |
| Total | 1056 | 594 | 97 | 55 | 7 | 753 | 70 | 28 | 238 | 20 | 29 | 287 | 16 |

*Without reference as to presence or absence of breast cancer.

Table III, 753 patients were dead, 238 were known to be alive. The status of 65 was unknown, but of these cases 29 had been followed for 10 years and 20 for 5 years, so that the follow-up at 5 years was 98.5 per cent complete. Since all patients seen after 1944 could not have been followed for 5 years, survival data concerning them were used to the nearest completed year of follow-up.

7. *Cause of death.* Death certificates, letters from other physicians and from relatives were examined in order to ascertain whether a patient died from or with carcinoma of the breast. Cases were recorded as having cancer of the breast at death when the evidence from these sources was positive. The great majority of patients died elsewhere than in the University Hospital. The overall autopsy rate was only 9.3 per cent.

### STATISTICAL METHODS

All conclusions in which significant differences are claimed were supported by statistical analyses of the relevant groups.

1. Data regarding distribution of cases according to stages and by time periods, side of lesion, and survival after various forms of therapy were statistically analyzed for differences by the $X^2$ test for homogeneity (8). The level of significance used was $P=0.01$. Thus, a difference was accepted as significant if the occurrence by chance was possible at the 1 per cent level or less.

2. Differences of means, such as age, were tested by using the standard error of the difference between two means. Differences were considered as significant if the observed difference was at least 2.5 times the standard error of the difference.

3. Significance of differences between rates was tested by using the theory of simple sampling of attributes (26), where p is the proportion of success and 1—p the proportion of failure in a sample of n cases. An observed difference was considered significant when it was at least 2.5 times the standard error of the difference.

4. Delay in months between reported onset and treatment or admission was analyzed by testing distributions of delay for differences and similarity between stages, using the $X^2$ test. Because of the skewness of data, median delay instead of mean delay was calculated for each stage. Significance of differences between these medians was determined. Percentage distributions of delay in months were calculated and analyzed for each stage.

5. For determinations of survival, the data were divided into groups of single complete years, and tabulated by single years until the last complete year for which follow-up was possible. Thus, all cases treated before 1940 could be followed for a progressively decreasing number of years. Only patients definitely known to be alive at the end of each year were recorded in the numerator of any group. In order to obtain the survival rate, the number of cases known to be alive was divided by the number of all cases that could have been exposed to risk, including untraced cases. There were only 16 cases who were lost to follow up before 5 years, so that differences between minimum and maximum rates were inconsequential.

### ANALYSIS OF DATA FOR HOMOGENEITY

The total data on 1,056 cases were divided into 6 chronological periods, 1918 to 1924, 1925 to 1929, 1930 to 1934, 1935 to 1939, 1940 to 1944, and 1945 to 1947, and by the four stages of the disease (Table I).

The distribution of stages during the 6 chronological periods is not homogeneous. All stages of the periods 1918 to 1924 and 1945 to 1947 and stage IV of all years contributed heavily to deviations from what was expected if the stages had been homogeneous with respect to time periods. However, there are no consistently significant changes in distribution of stages with time. No evidence was present that more women with early cancer of the breast were seen and recorded at the University Hospital in recent years as compared with 30 years ago.

The ages of women at onset and at admission, during the 6 periods, were analyzed by stages of the disease. No statistically significant differences nor trends were found during the 30 year period.

The delay, by stages and by chronologic periods, was examined. No statistically significant trends were present. The data con-

cerning delay failed to demonstrate that there is now earlier acceptance of medical attention by women with breast cancer in this area than there was in 1920.

The distribution of cases showing involvement of the right or left breast, the outer or the inner quadrants of the breast, and the number of cases with bilateral carcinoma, were found to be distributed homogeneously throughout the 6 periods.

On the basis of these analyses of distribution by stages, age at onset and admission, delay, location of the lesion and bilateral involvement, the total data, divided by stages, could be considered as representing a similar population during the whole period of survey. Thus, women with breast cancer seen at the University Hospital in 1918 were similar in respect to these factors to women with breast cancer observed 30 years later. The data were then examined by the type and the effect of therapy during the 30 year period.

Radical mastectomy without roentgen therapy remained the treatment of choice in stage I cancer throughout the 30 year period: 205 patients had radical mastectomy only, and in 41 of the patients some form of roentgen therapy was also given. Simple mastectomy was performed on 29 patients; these were of advanced age or had other contraindications to extensive surgery.

The choice of treatment for stage II disease was almost the same as for stage I, except for a higher percentage of patients receiving radiation. Before 1930, only 2 of 78 patients had roentgen therapy, whereas after 1935, 43 per cent of the patients were thus treated.

In stage III cancer, radical mastectomy without radiation was performed in 41 of 51 patients seen before 1930. After 1935, 36 per cent of the patients had either roentgen therapy alone or roentgen therapy combined with simple mastectomy.

In stage IV, treatment was directed toward palliation in all but 6 cases. Forty per cent of the patients received no treatment.

It was evident that the clinical concepts regarding the role of radical mastectomy in advanced breast cancer, and the role of radiation treatment had undergone several modifications. Of 219 patients treated before 1930, only 6 are recorded as having received roentgen therapy as defined here. During the 1930 to 1944 period, 40 per cent of 680 patients received radiation treatment. After 1944, radiation was employed in 27 per cent of 157 cases.

No systematic plan was followed in selecting patients for radiation, and the criteria and degree of selection are unknown. Moreover, of a total of 143 cases that received radiation before surgery, in 114 more than 6 weeks elapsed between the completion of radiation and the operation. Of a total of 109 patients who received radiation after surgery, radiation was started later than 1 month after operation in 49. When the data were divided according to type of roentgen therapy received, and according to the stage of the disease, the groups were too small for separate statistical analysis. Perforce, all such groups, within stages, were combined for subsequent analyses.

In order to demonstrate whether the results of treatment during the early periods could be validly compared with the results during recent years, analysis was made of the 5 year survival rates in stages I and II treated by radical mastectomy only during the 6 chronological periods. No significant differences or trends were found.

This review indicated that patients with cancer of the breast seen at the University of California Hospital during the period 1918 to 1947 were homogeneous in respect to treatment by radical mastectomy and 5 year survival, and that results of treatment in specific stages could be validly combined for further analyses without regard to the chronological period of the cases.

## FREQUENCY

The frequency of carcinoma of the breast in the female population admitted to the University Hospital is given in Figure 1. Previous examination (24) showed that the distribution of the University Hospital population according to age in decades after 30 years of age closely parallels the distribution of the general population of the United States. The estimated overall frequency rate of cancer of the breast was 11.9 per 1,000 female patients, rising steadily from 0.2 before

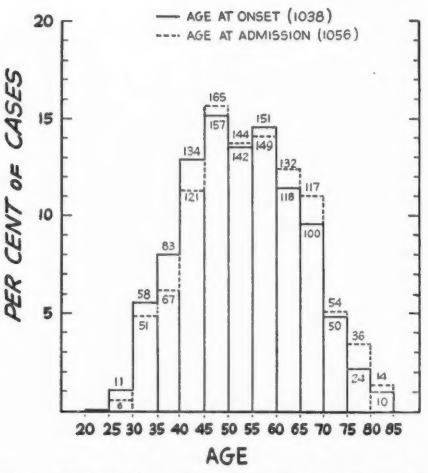


Fig. 2. Distribution of female patients with cancer of the breast against age at apparent onset (1,038 cases) and at admission (1,056 cases). The age at onset was unknown in 18 cases. Numbers refer to actual numbers of cases observed.

age 30 to 29.8 during the 60 to 69 age period and then decreasing to 25.3 above age 70.

Forty-four women developed cancer of both breasts, the involvement of the second breast being from all evidence apparently an independent, second neoplasm. This is a frequency of 4.2 per cent among 1,056 women with mammary cancer, or almost four times the frequency of breast cancer among the total female hospital population. The frequency is minimal because 238 women are still alive, and thus have not had complete exposure to the risk of developing a second primary mammary cancer. In comparison, 28 women have had other malignant neoplasms of other types, a frequency of 2.6 per cent.

TABLE IV.—AGE AT ONSET AND AT ADMISSION

| Stage | Age at onset* | | Age at admission | |
|---|---|---|---|---|
| | No. of cases | Mean age years | No. of cases | Mean age years |
| I | 333 | 52.7±0.65 | 334 | 53.4±0.64 |
| II | 296 | 51.5±0.66 | 299 | 52.3±0.66 |
| III | 310 | 53.7±0.67 | 314 | 55.4±0.70 |
| IV | 99 | 51.5±1.24 | 109 | 55.4±1.15 |

*Unknown in 18 cases

The data indicate that the most common second neoplastic lesion in women with cancer of the breast is cancer of the other breast. The possibility of developing cancer of the second breast among women with cancer of one breast is considerably higher than the chances for women in the general population to develop cancer of one breast (6).

It has been pointed out by Buck and Clemmesen that cancer of the left breast is more frequent than that involving the right breast. In their data, 2,117 of the tumors were on the left side as compared with 1,908 on the right. The present figures (Table II) of 544 on the left and 509 on the right, including the first breast involved in bilateral cases, are almost identical with the ratio found in Denmark, England, and Switzerland. Although analysis of the present figures fails to demonstrate that this difference is statistically significant, it is in conformity with the European data.

### AGE AT ONSET AND AT ADMISSION

Table IV and Figure 2 show the ages at apparent onset and at admission to the hospital or clinic. The range of age at onset was from 25 to 85 years of age.

Analysis of the age at onset shows no significant difference between the four stages. This indicates that the single factor of age at onset is not important of itself in the distribution of women according to the stage of disease. In other words, older women as well as young women may develop a rapidly growing, metastasizing neoplasm.

In contrast to the age at onset, there is significant difference between the age at admission of patients with stages I and II of the disease, on the one hand, and stages III and IV, on the other. This difference is a function of the delay period, since the age at admission is equal to the age at onset plus the delay.

### DELAY

Table V and Figure 3 present data on the delay period, according to the stages of the disease, as measured by months from apparent clinical onset to time of treatment or admission. This was determinable in 1,038 of 1,056 cases. Of these, 97 per cent first detected the lump or other abnormality of the breast them-

selves, and only 3 per cent of the tumors (32 cases) were first found by physicians.

Statistical analysis shows significant differences between per cent of cases stages I and II with delays of less than 2 months (34.5 versus 25.3) and with delays of from 6 to 12 months (14.7 versus 22.6). There is no significant difference between the two stages when patients with delays of over 12 months are considered. The median delay of 4 months for stage I is not significantly lower than the median delay of 5.5 months for stage II. The differences in distribution of delay between stages III and IV, and between either of these and stages I or II, are statistically highly significant.

The results of the analyses indicate that delay has a definite influence in determining the stage of the disease that is found at admission, including the occurrence of axillary metastases from smaller lesions that places women into stage II of the disease. It is true, and not contradictory, that even a long delay may not alter the stage of the disease or the prognosis regarding survival. Conversely, the shortest delay does not exclude the presence of metastases. Other things being equal, however, the longer a tumor is present, the greater the opportunity exists for the growth and spread of the neoplasm.

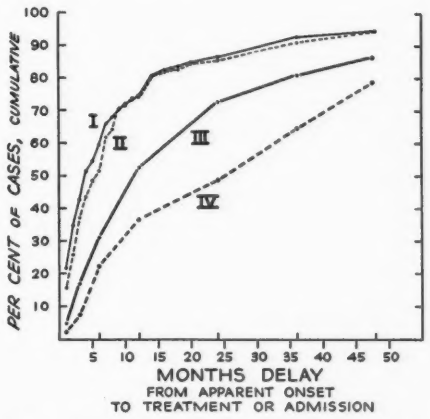


Fig. 3. Distribution of 1,038 female patients, by the stage of disease at treatment, or admission, against the delay from apparent onset. The percentage of cases in any stage at any specific delay period cumulates all cases up to that period (see Table V).

### ANALYSIS OF SURVIVAL

*Survival from apparent onset.* Table VI gives the survival from apparent onset of 1,038 women with breast cancer divided by the stages of the disease at admission. Figure 4 presents these data graphically. Superimposed on the figure are the survival rates of the general female population at the age of 52 years during the 1939 to 1941 period in the United States (10), and the survival rate in untreated women with cancer of the breast as determined in 516 cases by Greenwood in England and on 100 women by Daland in the United States. There are significant differences in survival rates among the four stages in terms of the character of the curves. The difference between the curve for the general female population and the curve for women with stage I cancer persists after 5 years. This indicates a continued increased mortality rate in stage I cancer of the breast following the completion of the classical 5 year period. The continued drop is more evident in women with stage II and stage III disease.

Stage III shows a higher survival than stage IV or the untreated groups although the differences in each successive year are not consistently significant.

There is no difference between survival of women with stage IV disease and survival in untreated cases of Greenwood and of Daland.

TABLE V.—DELAY FROM APPARENT ONSET TO TREATMENT OR ADMISSION, BY STAGES OF THE DISEASE

| Delay months | Stage of disease | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | | II | | III | | IV | |
| | No. | Per cent | No. | Per cent | No. | Per cent | No. | Per cent |
| 1 | 71 | (21.3) | 47 | (15.9) | 15 | ( 4.8) | 2 | ( 2.0) |
| 1– 2.9 | 70 | (21.0) | 63 | (21.2) | 38 | (12.3) | 5 | ( 5.1) |
| 3– 5.9 | 57 | (17.1) | 42 | (14.2) | 43 | (13.9) | 15 | (15.1) |
| 6–11.9 | 49 | (14.7) | 67 | (22.6) | 67 | (21.6) | 14 | (14.2) |
| 12–23.9 | 40 | (12.1) | 34 | (11.5) | 62 | (20.0) | 12 | (12.1) |
| 24–35.9 | 21 | ( 6.3) | 17 | ( 5.8) | 26 | ( 8.4) | 16 | (16.1) |
| 36 | 25 | ( 7.5) | 26 | ( 8.8) | 59 | (19.0) | 35 | (35.4) |
| Total | 333 | (100.0) | 296 | (100.0) | 310 | (100.0) | 99 | (100.0) |
| Median, in months (by interpolation) | 4.0±0.82 | | 5.5±0.63 | | 11.5±1.04 | | 25.0±1.73 | |

TABLE VI.—SURVIVAL IN CANCER OF THE BREAST FROM APPARENT ONSET, DIVIDED BY STAGES OF DISEASE AT ADMISSION

| Years after onset | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Stage I** | | | | | | | | | | |
| No. of cases alive | 326 | 311 | 273 | 246 | 212 | 189 | 165 | 140 | 121 | 100 |
| Total no. of cases | 333 | 333 | 315 | 294 | 279 | 256 | 236 | 210 | 185 | 160 |
| Per cent survival | 97.9 | 93.4 | 86.7 | 83.7 | 76.0 | 73.8 | 70.0 | 66.7 | 65.4 | 62.5 |
| Standard error of per cent | ±0.8 | ±1.4 | ±1.9 | ±2.2 | ±2.6 | ±2.7 | ±3.0 | ±3.2 | ±3.5 | ±3.8 |
| **Stage II** | | | | | | | | | | |
| No. of cases alive | 289 | 244 | 202 | 171 | 133 | 110 | 88 | 68 | 54 | 47 |
| Total no. of cases | 296 | 296 | 285 | 280 | 267 | 252 | 230 | 201 | 184 | 171 |
| Per cent survival | 97.6 | 82.4 | 70.9 | 61.1 | 49.8 | 43.6 | 38.3 | 33.8 | 29.3 | 27.5 |
| Standard error of per cent | ±0.3 | ±2.2 | ±2.7 | ±2.9 | ±3.1 | ±3.1 | ±3.2 | ±3.3 | ±3.4 | ±3.4 |
| **Stage III** | | | | | | | | | | |
| No. of cases alive | 287 | 226 | 162 | 115 | 85 | 63 | 47 | 39 | 32 | 22 |
| Total no. of cases | 310 | 310 | 287 | 265 | 246 | 227 | 209 | 190 | 184 | 168 |
| Per cent survival | 92.6 | 72.9 | 56.4 | 43.4 | 34.6 | 27.8 | 22.5 | 20.5 | 17.4 | 13.1 |
| Standard error of per cent | ±1.5 | ±2.5 | ±2.9 | ±3.1 | ±3.0 | ±3.0 | ±2.9 | ±2.9 | ±2.8 | ±2.6 |
| **Stage IV** | | | | | | | | | | |
| No. of cases alive | 81 | 59 | 38 | 28 | 21 | 13 | 13 | 10 | 8 | 7 |
| Total no. of cases | 99 | 99 | 92 | 91 | 90 | 88 | 82 | 81 | 71 | 66 |
| Per cent survival | 81.8 | 59.6 | 41.3 | 30.8 | 23.3 | 14.8 | 15.8* | 12.3 | 11.3 | 10.6 |
| Standard error of per cent | ±3.9 | ±4.9 | ±5.1 | ±4.8 | ±4.4 | ±3.8 | ±4.0 | ±3.6 | ±3.8 | ±3.8 |

*No additional deaths occurred in the 7th year among 13 survivors of the 6th year while only 82 cases were exposed to risk in the 7th year as compared with 88 cases in the 6th year.

*Survival after treatment or admission.* Table VII indicates the survival rates in the total 1,056 cases. The date of operation was used in the determinations for women who underwent mastectomy; among women who received x-ray treatment only, the date of initiation of this treatment was used, whereas in stage IV and in some patients who received only palliation or no treatment, survival was measured from the time of admission for the breast condition. The data which are plotted in Figure 5 include the survival of the general female population at the age of 53 years (10).

The overall data include a total of 751 women who underwent radical mastectomy. There were 6 postoperative deaths, or a mortality of 0.8 per cent. A total of 153 women had simple mastectomy, with or without axillary dissection, with 1 postoperative death, or a mortality of 0.6 per cent. During the same period, 312 women received full courses of x-ray treatment, and 2 women died of complications directly attributable to the treatment, for a mortality of 0.6 per cent.

There are statistically significant differences between the survival rates of all four stages, at 5 and at 10 years after treatment or admission.

For the remaining analyses, use was made only of cases seen through 1944, which had full 5 year follow-up on January 1, 1950. In analyses of effects of therapy, all postoperative deaths and untraced cases are included. For analysis of certain possible factors influencing the results, only cases belonging to groups under consideration are included.

*Effect of type of treatment.* Table VIII presents the 5 year survival rates by stages and by major forms of treatment.

Although the results with radical operation alone among cases in stage I show a higher survival than in the group that also received radiation at some time before or after radical surgery, the difference is not statistically sig-

TABLE VII.—SURVIVAL IN CANCER OF THE BREAST, FROM TREATMENT (STAGE I–III) OR ADMISSION (STAGE IV)

| Years after operation or admission | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Stage I** | | | | | | | | | | |
| No. of cases alive | 321 | 294 | 265 | 234 | 203 | 177 | 154 | 131 | 110 | 93 |
| Total no. of cases | 334 | 334 | 316 | 295 | 280 | 257 | 237 | 211 | 186 | 161 |
| Per cent survival | 96.1 | 88.0 | 83.9 | 79.3 | 72.5 | 68.9 | 65.0 | 62.1 | 59.1 | 57.8 |
| Standard error of per cent | ± 1.0 | ± 1.8 | ± 2.1 | ± 2.4 | ± 2.7 | ± 2.9 | ± 3.1 | ± 3.3 | ± 3.6 | ± 3.9 |
| **Stage II** | | | | | | | | | | |
| No. of cases alive | 275 | 223 | 174 | 144 | 114 | 90 | 71 | 59 | 46 | 42 |
| Total no. of cases | 299 | 299 | 288 | 283 | 270 | 255 | 233 | 204 | 187 | 173 |
| Per cent survival | 92.0 | 74.6 | 60.4 | 50.9 | 42.2 | 35.3 | 30.5 | 28.9 | 24.6 | 24.3 |
| Standard error of per cent | ± 1.6 | ± 2.5 | ± 2.9 | ± 3.0 | ± 3.0 | ± 3.0 | ± 3.0 | ± 3.2 | ± 3.1 | ± 3.3 |
| **Stage III** | | | | | | | | | | |
| No. of cases alive | 238 | 155 | 96 | 71 | 46 | 31 | 24 | 16 | 11 | 10 |
| Total no. of cases | 314 | 314 | 291 | 269 | 250 | 231 | 213 | 194 | 188 | 172 |
| Per cent survival | 75.8 | 49.4 | 33.0 | 26.4 | 18.4 | 13.4 | 11.3 | 8.2 | 5.8 | 5.8 |
| Standard error of per cent | ± 2.4 | ± 2.8 | ± 2.8 | ± 2.7 | ± 2.4 | ± 2.2 | ± 2.2 | ± 2.0 | ± 1.7 | ± 1.8 |
| **Stage IV** | | | | | | | | | | |
| No. of cases alive | 37 | 12 | 2 | 1 | 0 | — | — | — | — | — |
| Total no. of cases | 109 | 109 | 104 | 103 | 99 | — | — | — | — | — |
| Per cent survival | 33.9 | 11.0 | 1.9 | 1.0 | 0 | — | — | — | — | — |
| Standard error of per cent | ± 1.4 | ± 3.0 | ± 1.3 | ± 0.3 | — | — | — | — | — | — |

nificant. No other treatment rates were calculated because of the small number of cases.

In stage II the survival rate following radical mastectomy only is lower than that following radical operation supplemented by radiation. Again the difference is not statistically significant. The data on simple mastectomy are, of course, too limited to be used statistically.

In stage III, the survival rate following radical mastectomy alone is lower, although not significantly so, than the rates following any other form of therapy which included radiation.

In stage IV, no patient survived longer than 4 years after admission or initiation of treatment.

It has already been stated that analysis of survival following radical mastectomy, when divided by the stages of the disease, shows no significant differences during the chronological periods of the 30 years studied. If, however, all cases treated by radical mastectomy, with or without radiation, are grouped together by 5 year periods without regard to staging, a trend toward progressively higher survival figures is obtained, from 41.4 per cent in the 1918 to 1924 period to 54.5 per cent during the 1940 to 1944 period. Before 1930, the survival rate in 191 women undergoing radical surgery was 42.4 per cent; after 1930 52.3 per cent of 430 women were alive at 5 years. The difference is statistically significant, and reflects more rigorous selection of operable cases so that progressively fewer women with advanced disease underwent radical mastectomy. This is verified by the following figures: in 1918 to 1924, only 29.8 per cent of all cases receiving radical mastectomy were in stage I as compared with 45.1 per cent in 1940 to 1944; before 1930, 36.6 per cent were in stage I and after 1930, 40.9 per cent were in stage I. Further, in 1918 to 1924, 47.2 per cent were in stage II and 23.0 per cent in stage III while in 1940 to 1944, 39.4 per cent were in stage II and only 15.5 per cent in stage III.

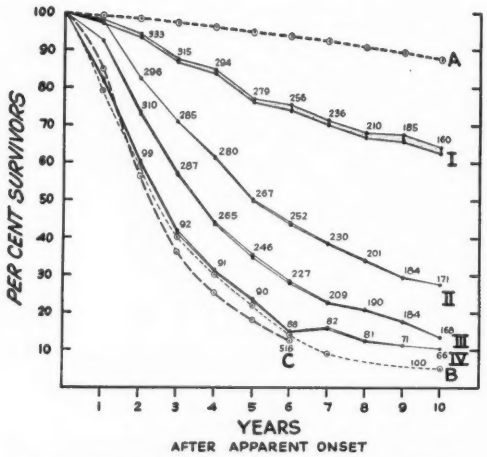


Fig. 4. Survival of 1,038 female patients with cancer of the breast after apparent onset, by stages of the disease. The numbers at points indicate number of patients contributing to the value, and upper double lines indicate values obtained if untraced cases are removed from the denominator. Line *A* is the survival rate of the general female population at the age of 52 years, during the 1939 to 1941 period in the United States (10). Line *B* is the survival rate in 100 untreated women with cancer of the breast as determined by Daland. Line *C* is the survival rate in 516 untreated women with cancer of the breast as determined by Greenwood.

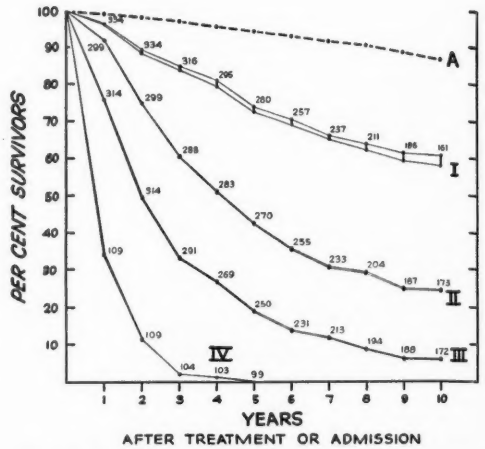


Fig. 5. Survival of 1,056 female patients with cancer of the breast after mastectomy. In women who received x-ray treatment only, the date of initiation of treatment was used, and in women who received no treatment, survival was measured from time of admission for the breast condition. The numbers at points indicate number of patients contributing to the value, and upper double lines indicate values obtained if untraced cases are removed from the denominator. Line *A* demonstrates the survival rate of the general female population at the age of 53 years, during the period of 1939 to 1941 in the United States (10).

The data fail to demonstrate any consistent or significant increase in survival rate by the supplementation of radiation in the treatment of mammary cancer. Possible differences are obscured by the small number of cases available for analysis, and the forced grouping of perhaps noncomparable methods of radiation therapy.

*Deaths from cancer within 5 years.* It has been demonstrated that significant differences in survival are obtained when the data are divided according to the four stages of the disease. The survival above the rate seen in women with untreated mammary cancer is usually assumed to be the result of the treatment afforded to the patients. It is possible also that the process of staging itself groups patients with tumors of "low malignancy" in stage I and those with tumors of "high malignancy" toward stages III and IV.

An approach toward the estimation of the role of the biological properties of the neoplasms and the possible host-resistance factors is afforded by considering women who are treated at different stages of the disease and who die of the recurrence, metastasis, or other direct effects of the neoplasm. Thus, if the degree of malignancy inherent in the tumor is the chief determinant in the staging and in the results of treatment, women with stage I disease who die of cancer should live longer than women with more advanced disease in whom the disease is not eradicated or controlled.

The distribution of mortality in 6 month periods was analyzed for women who died of breast cancer during the first 5 years after apparent onset and after treatment or admission. The data are presented in Table IX.

There is a consistent trend toward lower mean survival in women with stage I to stage IV disease, as gauged from apparent onset. There is a statistically significant difference between stage I and stages III and IV, although the difference between stage I and stage II is not significant. There is also a significant difference between stages II and IV.

TABLE VIII.—FIVE YEAR SURVIVAL FOLLOWING VARIOUS FORMS OF TREATMENT (DATA OF 1918 TO 1944, INCLUSIVE)

| Treatment | | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|---|
| Radical mastectomy | No. cases alive | 158 | 70 | 14 | 0 |
| | Total no. cases | 205 | 179 | 87 | 3 |
| | Per cent survival | 77.1±2.9 | 39.1±3.6 | 16.1±3.9 | — |
| Radical mastectomy plus x-rays* | No. cases alive | 27 | 27 | 11 | 0 |
| | Total no. cases | 41 | 58 | 47 | 1 |
| | Per cent survival | 65.8±7.4 | 46.6±6.5 | 23.4±6.2 | — |
| Simple mastectomy | No. cases alive | 9 | 7 | 2 | 0 |
| | Total no. cases | 19 | 12 | 18 | 11 |
| | Per cent survival | — | — | — | — |
| Simple mastectomy plus x-rays* | No. cases alive | 8 | 10 | 8 | 0 |
| | Total no. cases | 10 | 18 | 33 | 10 |
| | Per cent survival | — | — | 24.2±7.5 | — |
| X-rays* | No. cases alive | 1 | 0 | 9 | 0 |
| | Total no. cases | 2 | 2 | 49 | 11 |
| | Per cent survival | — | — | 18.4±5.5 | — |
| Palliative or none | No. cases alive | 0 | 0 | 2 | 0 |
| | Total no. cases | 3 | 1 | 16 | 63 |
| | Per cent survival | — | — | — | — |
| Total | No. cases alive | 203 | 114 | 46 | 0 |
| | Total no. cases | 280 | 270 | 250 | 99 |
| | Per cent survival | 72.5±2.7 | 42.2±3.0 | 18.4±2.4 | — |

*All cases received adequate radiation therapy as defined, whether preoperative or postoperative or radiation only.

When measured from treatment or admission, there is the same trend of shorter mean survival from stage I to stage IV. The differences between stage I and stages III and IV, and stage II as compared with stages III and IV are statistically significant, although the difference between stages I and II is not.

The analysis indicates that staging in itself tends to group cases with slower-killing neoplasms into stage I, and the more malignant tumors toward stages III and IV.

*Factors possibly modifying survival.* Data on women with stages I and II disease who were treated by radical mastectomy only were used for analyses of certain factors that may have modified survival. In these analyses, postoperative deaths and untraced cases are not included.

The possible influence of the operator was investigated. No significant difference was found in survival after operations performed at the University Hospital by the 6 principal surgeons. The total 5 year survival in 156 patients with stage I disease was 124 or 79.5 per cent, and in 132 patients with stage II disease it was 54, or 40.9 per cent. In comparison, 49 operations in stage I cancer and 47 operations in stage II cancer that were performed by the resident staff or other surgeons

TABLE IX.—SURVIVAL OF WOMEN DYING OF CANCER OF THE BREAST WITHIN FIVE YEARS AFTER APPARENT ONSET, AND AFTER TREATMENT OR ADMISSION

| Stage | From apparent onset | | From treatment or admission | |
|---|---|---|---|---|
| | No. cases | Survival, months | No. cases | Survival, months |
| I | 41 | 35.6±2.7 | 48 | 32.7±2.4 |
| II | 107 | 32.1±1.4 | 122 | 27.2±1.5 |
| III | 143 | 28.2±1.1 | 177 | 20.7±1.1 |
| IV | 67 | 25.2±1.8 | 87 | 9.7±0.9 |
| Untreated* | 78 | 26.4±1.8 | — | — |

*Data of Daland.

yielded survivals of 34 (69.4 per cent) and 16 (34.0 per cent), respectively. In view of the small number of cases involved, these differences are not statistically significant.

The groups were divided according to the location of the lesion in the outer or the inner quadrants of the breast. In stage I, the 5 year survival in 130 women with outer quadrant lesions was 101, or 77.7 per cent; for inner quadrant lesions, 44 of 53 women, or 83.0 per cent, were alive at the end of 5 years after operation. In stage II, the 5 year survival in 113 women with outer quadrant lesions was 51, or 45.1 per cent, as compared with 12 of 37 women, or 32.4 per cent with cancer in the inner quadrant. The data show no significant differences, and fail to substantiate a poorer prognosis for neoplasms in the inner quadrants of the breast (2).

The groups were divided according to the delay from presumed onset to operation. There were no consistent trends or differences in survival. Of 140 women with stage I disease whose delay was up to 6 months, the 5 year survival was 108, or 77.1 per cent. In 62 women delaying 7 months and over, 50, or 80.6 per cent, survived 5 years. In stage II, 115 women had a delay period of up to 6 months, with survival of 43, or 37.4 per cent; 63 women delayed for over 6 months, and of these 27, or 42.8 per cent, were alive at the end of 5 years after operation. The data show no significant effect of delay upon survival, so long as the cases remain in a particular stage of the disease.

The groups were then divided according to the age of the patient, by decades, at operation. There were no consistent trends nor differences in survival among successive age groups. In stage I, 66 of 85 women operated upon at ages under 50 years were alive at 5 years, for a survival of 77.6 per cent. Of 117 women operated upon at the age of 50 and over, the 5 year survival was 91, or 77.8 per cent. In stage II, 82 women were operated upon before the age of 50, with a 5 year survival rate of 41.5 per cent. Of 97 women operated upon after the age of 50 years, 37.1 per cent survived 5 years. Thus, a poorer prognosis among younger women is not substantiated by these data (23).

## DISCUSSION

The foregoing analyses have shown that the survival among women with cancer of the breast is dependent upon the anatomical extent of the disease at the time of treatment. The extent of the disease is determined primarily by the biologic properties of the neoplasm and possible host-resistance factors, and by the delay from apparent onset to treatment. The survival from operation at 5 years among women with relatively small neoplasms without clinical or pathological evidence of metastases was 72.5 per cent. The survival was 42.2 per cent when metastases were found in the axillary lymph nodes, and 18.4 per cent when more extensive disease was present. With distant metastases, there were no survivors. The survival at 5 years of all cases, of which 68 per cent had metastases, and including all untraced and untreated patients, was 40.4 per cent.

Comparison was attempted of these data with the results published from four other centers, the Memorial Hospital (1) and the Presbyterian Hospital (11) in New York, the Mayo Clinic (14) in Rochester, and the Royal Infirmary (19) in Edinburgh. Such comparisons are not entirely satisfactory because no uniform method of staging or of recording the data was used. In addition, reports from two of the centers were concerned with results of radical mastectomy only, and did not indicate the total data.

Adair reported a survival of 78.6 per cent in 737 cases of breast cancer without axillary metastases, and thus presumably falling into stage I as defined here. The total data on 3,355 women yielded a survival of 39.6 per cent. This indicates that 78 per cent of the patients had metastatic disease at the time of treatment. The presentation suffers from the deletion of 453 additional cases because of refusal of treatment, untraced cases, and cases stated to have died of "other causes without recurrence." There are no significant differences between Adair's figures and the present data, particularly when the indeterminate patients are taken into consideration.

Harrington reported survival following radical mastectomy on women with unilateral carcinoma of the breast, of which 61 per cent

had metastases. The survival at 5 years among 2,059 patients without metastases was 75.7 per cent, and in 3,348 women with metastases the survival was 30.4 per cent. The survival in the total group, and not including inoperable cases, was 47.6 per cent. This may be compared with the survival in the present series of 45.4 per cent among 800 women in stages I, II and III, although stage III includes approximately 50 per cent of inoperable cases. No significant differences between Harrington's figures and the present data are demonstrated.

Haagensen showed a survival of 74.3 per cent among 185 women with disease limited to the breast on whom radical mastectomy was performed. In 381 patients with axillary involvement who were treated by radical mastectomy, the survival was 38.3 per cent. Thus, in a group selected for operability and in which 70 per cent of the patients had metastatic disease, the 5 year survival was 50 per cent. Comparisons with the present data show no significant differences.

It may be concluded that the 5 year survivals at the University of California Hospital typify quite closely the results being achieved in other large surgical centers in the United States. The consistency of the data suggests that the condition of the patients being treated, the biologic properties of the tumors, and the treatment are rather monotonously uniform when considered on a group basis.

The present data, as reflecting the usual surgical experience in the United States, may be compared with the controversial results published by McWhirter who reported that the combination of simple mastectomy and immediate postoperative radiation yielded better survival at 5 years than radical mastectomy. Of a total 1,345 patients, 757 were designated as operable, whereas 389 had advanced disease without distant metastases. It was estimated that the incidence of axillary metastases in the operable group was 60 per cent, so that in the total series 77 per cent had metastases. The 5 year survival on all patients was calculated as 43.7 per cent, but 459 patients actually followed for the full 5 years yielded 42.9 per cent, and this group was stated to be "less patients who died from intercurrent disease." There is no significant difference between this survival and the survival of 40.4 per cent of the total 899 cases of the University of California series. Conversely, however, the overall survival following the simple mastectomy-immediate radiation method is certainly no lower than that achieved in the present series. This is particularly true since the proportion of cases with metastatic disease was higher in the Edinburgh series than in the California data. Further examination of McWhirter's results indicates that, if his operable cases are comparable with stages I and II, the 5 year survival is 62.1 and 57.6 per cent, respectively. Again, the difference is not statistically significant, but is certainly not lower in Edinburgh. If McWhirter's advanced cases are compared with stage III, the 5 year survivals are 29.0 per cent and 18.4 per cent, respectively. This difference is statistically significant, and would indicate an increment in survival among patients with advanced disease. It is interesting that the survival of 80 patients of stage III treated by radical or simple mastectomy plus radiation at the University of California Hospital was 23.7 per cent, a value not significantly different from the survival recorded by McWhirter.

The conclusion that can be derived from these comparisons is that the results on all patients at 5 years reported by McWhirter are as good as any achieved by the accepted radical mastectomy, with or without radiation.

It is evident that McWhirter's technique is not merely one of a simple mastectomy followed by radiation. Special precautions are taken in regard to both the operation and the x-ray course. Perhaps the most important points are that the mastectomy is as limited as possible, whereas radiation is started within 2 weeks after operation, and a minimal tumor dose of 3,750 roentgens is given through 4 fields within a period of 3 weeks.

All stage I carcinomas of the breast should be curable by simple mastectomy. Deaths from cancer of the breast in stage I disease are really a measure of the clinical and pathological limitations in the detection of the

presence of metastasis. It would seem, therefore, that no woman with true stage I cancer of the breast would be endangered by the McWhirter procedure. The chief argument revolves about stage II disease, with limited axillary metastases. There are definite reasons why McWhirter's therapy should be favorably considered despite the demonstration that radiation following radical mastectomy does not yield a significant improvement over figures obtained by radical mastectomy alone. The dose of radiation used by McWhirter is higher than that used routinely in the United States. This is possible because such radiation is delivered to a field not deprived of its blood supply, with the pectoral muscles intact over the thoracic cage. It is well known that fibrosis and avascularity interfere with the effects of radiation. The theory that metastatic carcinoma in lymph nodes is not radiocurable has had severe setback from the studies of Wood and Boag.

The possibility that McWhirter's treatment would merely seal off metastases in radiation-induced fibrosis, to recur at dates later than 5 years, cannot be entirely countered except by actual 10 year figures that will become available from Edinburgh. A sharp drop in the figures, however, is most unlikely. A similar situation has existed in the comparison of many other types of therapy for many other types of neoplastic disease: the figures at 3, 4, 7, or 10 years, if based on sufficient numbers, remain proportionately the same (23).

In the discussion thus far, it has been tentatively assumed that the survival of women undergoing radical mastectomy or other treatment is attributable to the therapy. It was brought out that in such survival rates, cognizance must be made of the survival among presumably comparable untreated women. The 5 year survival of untreated patients as reported by Greenwood and by Daland is approximately 20 per cent after apparent onset, and approximately 15 per cent if a period of 1 year is assumed as the mean delay of all women from apparent onset to treatment. Thus, all statistics on survival at 5 years following therapy must be corrected for the expected 15 to 20 per cent survival among untreated patients. Allusion also has been made to the important role of the biologic properties of the tumor and the host-resistance factors, and the influence of these factors upon survival and upon the grouping of women within clinical and pathological stages of the disease.

Park and Lees in an excellent, thoughtful discussion of this problem, come to the conclusions that not only delay in treatment has not been demonstrated to affect the 5 year survival, but that it has not even been proved that the survival rate in cancer of the breast is affected by treatment at all. Variability in growth rate between different cancers combined with the use of a survival rate as a measure of cure may create an apparent cure rate which is partly or wholly fictitious. This problem is also indicated in the presentations of McKinnon and of MacDonald (17).

We agree with Park and Lees in that it is futile to speak of 5 year "cure" rates in cancer of the breast. At the best, at 5 years certain women can be stated to have no clinical evidence of recrudescence or metastasis of the neoplasm. Determination of survival rates which remove women presumably dying of causes other than cancer during any period also appears unjustified. Certainly if the local experience of autopsies on less than 10 per cent of the cases is general, such corrections must have a prohibitive degree of error. For these reasons, throughout this paper no reference is made to "cure" and only survival is considered.

We believe, however, that the data presented here clearly show that delay in treatment *has* a definite effect upon survival in cancer of the breast, and that the present methods of treatment do produce considerable salvage of women with mammary carcinoma.

On the basis of the data on delay available in Table V and on observed 5 year survival in Tables VII and VIII, determination can be made of the survival at 5 years that can be anticipated by the present methods for the treatment of cancer of the breast. Figure 6 shows the distribution of the stages

of the disease dependent on the delay from apparent onset to treatment. Even when the apparent delay is less than 1 month, 48 per cent of the women are found to have metastatic disease. If the 5 year survivals for the four stages of the disease are 73, 42, 18, and 0 per cent, respectively, the 5 year survival in this group is 55 per cent. There is a consistent and significant decrease in the number of women in stages I and II of the disease as the length of delay increases, and, conversely, an increase in the proportion of women in stages III and IV. Of women who delay treatment for over 3 years, only 17 per cent do not have evidence of metastatic disease, whereas 65 per cent are in the advanced stages with extensive local or distant metastases. Since the survival rate of women in any one stage is not affected by delay, survival from operation in this group is 28 per cent. Considering that 15 to 20 per cent of untreated women with cancer of the breast survive a comparable period, the total treatment in all women results in an increment in survival at 5 years of 35 per cent if no delay has occurred, and of 13 per cent if a delay of 3 years or more has occurred.

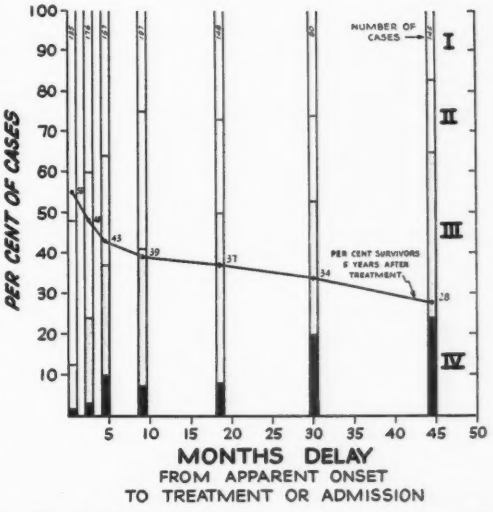


Fig. 6. The effect of delay upon the distribution of cases by stage of the disease, and upon the 5 year survival rates to be anticipated by proportional weighing of the observed survival rates for different stages. Bar graphs are placed at the middle of each delay period. With an apparent delay of less than 1 month, 48 per cent of the patients have metastases, and the 5 year survival in the whole group is 55 per cent. The survival of untreated women with cancer of the breast at 5 years after onset is 20 per cent.

The survival of patients following treatment in any specific stage of the disease has been shown to be independent of the apparent delay. Thus, the same proportions of patients in any stage were alive in the group that had delay of, say, less than 1 month and in the group that had delay of 3 years or more. It is obvious, however, that had women with a delay of 3 years undergone treatment within a month after onset, the group could not have included patients who died within 3 years after apparent onset.

What, then, would have been the survival if all women had had treatment within a month after apparent onset? The observed distribution by stages in the group with a delay of less than 1 month has been shown to be 52, 35, 11, and 2 per cent, respectively. If this distribution is applied to all other groups, 665 patients with delay of less than 1 year would have had a survival of 55 per cent. Groups with delay of 1, 2, or 3 years represent cases in which no deaths are included for these periods, so that the survivals at 4, 3, and 2 years for each stage must be applied and weighed according to the number of cases observed in the three groups. The calculations yield 5 year survivals in these groups of 62, 68, and 77 per cent. The overall survival at 5 years for all 1,038 cases, on the basis of these determinations, would have been 60 per cent. Thus, if all patients had had delay of less than 1 month, the 5 year survival would have been 60 per cent, or 20 per cent above the actual 40 per cent that was obtained in this series, and 40 per cent above the 20 per cent survival to be anticipated among untreated women.

It is evident, of course, that women who undergo treatment after a delay of less than 1 month presumably have had less than 1 month of life with the neoplasm, whereas women who enter with a delay of over 3 years have had at least 36 months of life with the neoplasm. Moreover, women who die of cancer during the 5 year period after

TABLE X.—MEAN SURVIVAL OF WOMEN WITH CANCER OF THE BREAST, FROM APPARENT ONSET TO FIVE YEARS AFTER TREATMENT, ACCORDING TO DELAY

| Delay months | Time before treatment* months | Mean survival period contributed by cases dying of breastcancer† months | Survival period contributed by cases alive at 5 years‡ months | Total mean survival period, per case months |
|---|---|---|---|---|
| 1 | 0 | 12.3 | 33.0 | 45.3 |
| 1– 2.9 | 1.0 | 13.1 | 28.8 | 42.9 |
| 3– 5.9 | 3.0 | 13.1 | 25.6 | 41.7 |
| 6–11.9 | 6.0 | 14.1 | 23.4 | 43.5 |
| 12–23.9 | 12.0 | 13.9 | 22.2 | 48.1 |
| 24–35.9 | 24.0 | 13.3 | 20.4 | 57.7 |
| 36 | 36.0 | 16.4 | 13.9 | 66.3 |

*Minimum of delay period, per case.
†Weighted by proportion of stages at interval (Table V) using mean survival by stages (Table IX).
‡Weighted by proportion of survival by stages (Table VIII) and distribution of cases by stages at interval (Table V).

treatment live for an average of 33, 27, 21, and 10 months, depending upon the stage of the disease at entry (see Table IX). These periods of survival were assumed to hold for all patients dying within 5 years. Thus, the total span of life in the average case includes the period of delay, the mean period of survival of patients who die during the 5 year period, and the survival contributed by the proportion of patients surviving the 5 year period. Table X presents the calculations made on this basis, and shows that up to 5 years after treatment or admission, the average patient with breast cancer lives for 45 months if there has been less than 1 month of delay, whereas if such treatment occurs after a delay of 3 years or longer, an average life span of 66 months is obtained.

These data should not be perverted toward the untenable supposition that delay is desirable for women with cancer of the breast, and that is not their meaning. The data do clearly show, however, the tremendous influence of the biologic properties of neoplasms upon the survival of the host. Consideration of data by delay of treatment, as well as within stage of the disease, groups or selects cases of rapidly growing, rapidly killing neoplasms toward one end of the scale, and of the slow growing, less fatal neoplasms toward the opposite end. These factors are of utmost importance in the correct evaluation of what is and what is not achieved by any particular form of treatment.

These conclusions indicate the limitations in the results relative to survival of women with cancer of the breast following surgery and the degree of improvement that is possible to achieve with full application of educational and other measures that would shorten delay and increase acceptance of treatment by all women with small masses in the breast. Such measures undoubtedly will improve the total survival, as has been demonstrated in this study. The size of the tumor and the presence of metastases is, in part, a function of the length of time a tumor has been present, as well as of the biologic properties of the neoplasm. Results of full application of the presently known clinical methods of detecting and treating this disease however, appear to be limited to a total yield of approximately 60 per cent 5 year survival.

Further modifications in surgical techniques, such as anatomical extension of the classical operation, conceivably could yield some improvement in the results. Since radiation therapy following simple removal of the breast has been demonstrated to achieve results entirely comparable with the results of radical surgery, this also appears to be a logical and promising area for further investigation at other centers. The situation also enforces the view that in the eventual picture, research on the biological and biochemical methods of detection and treatment of cancer of the breast is the only means by which a more optimistic outlook can be eventually justified and incontroversially supported.

## SUMMARY

Data on all female patients with cancer of the breast recorded at the University of California Hospital during a 30 year period, 1918 to 1947, inclusive, were reviewed and statistically analyzed.

The total data on 1,056 patients were examined for homogeneity and variance, and were found to be homogeneous during the period of study. The cases were divided into

four anatomical stages of the disease. Data relative to age and delay were analyzed, with emphasis upon the relationship of these factors to survival. The data were analyzed in regard to survival at 5 years, by stage of the disease and by the type of treatment, after apparent onset and after treatment.

The 5 year survival of 280 women with disease localized to the breast (stage I) was 72.5 per cent. In 270 women with metastases to the axillary lymph nodes (stage II) it was 42.2 per cent. In 250 women with advanced disease (stage III), the 5 year survival was 18.4 per cent, and none of 99 women with distant metastases (stage IV) was alive 5 years after admission. The 5 year survival of all 899 women was 40.4 per cent.

The data were compared with results reported from three other surgical centers in the United States and in Edinburgh. No significant differences were elicited.

Survival of women with cancer of the breast is dependent upon the anatomical extent of the disease at time of treatment, which is determined primarily by the biologic properties of the neoplasm and possible host-resistance factors, and by the delay from apparent onset to treatment.

Age at onset and operation, location of the neoplasm in the breast, and delay do not affect significantly the 5 year survival when the cases are grouped by the stages of the disease. The ratio of stages changes with delay, however, and the process of staging itself tends to group women with neoplasms of different biologic properties.

It is concluded that with present methods of detection and treatment of cancer of the breast, if all patients had delay of less than 1 month from apparent onset to treatment, a 5 year survival of 60 per cent could be achieved. This is 20 per cent above the actual 40 per cent obtained in this series, and 40 per cent above the 20 per cent survival to be anticipated among women with untreated breast cancer.

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# ANTIBACTERIAL SUBSTANCES IN HUMAN SEMEN AND PROSTATIC FLUID

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IT HAS been reported that human semen and prostatic fluid obtained from dogs possess the capacity of inhibiting the growth of certain bacteria that cause infections of the genitourinary tract. Youmans and his associates found that dog prostatic fluid inhibited the growth of Staphylococcus aureus, Escherichia coli, and Streptococcus hemolyticus and also produced some inhibition of the growth of Streptococcus viridans and Neisseria gonorrhoeae. In studies with human subjects, Rozansky and his co-workers reported that human semen had a marked inhibitory action on three strains of Staphylococcus aureus. The present study was undertaken to determine the antibacterial activity of human semen and prostatic fluid against a number of common genitourinary tract pathogens and to ascertain the nature of these inhibitory factors.

## MATERIALS

*Semen.* Semen was collected from 6 normal healthy medical-student donors and from 13 healthy individuals who brought samples in for analysis in the sterility clinic of the Strong Memorial Hospital. Seven semen samples had low sperm counts (below 60 million per c.c.) and 1 specimen was azoospermic. The material was collected in clean receptacles after manual expression and brought to the laboratory immediately. The samples were allowed to liquefy for 4 hours and used directly, or were frozen and stored in the deep freeze at −15 degrees F. for future experimentation.

*Prostatic fluid.* Prostatic fluid was collected from 50 persons in the genitourinary clinic of the Strong Memorial Hospital by prostatic massage. Individuals included were those who exhibited no genitourinary disease and patients who showed cystitis, prostatitis, benign prostatic hypertrophy, and carcinoma of the prostate. The material was collected in sterile glass tubes and tested immediately, or stored in the deep freeze at −15 degrees F. until used.

All samples obtained were cultured on blood agar plates to determine the presence and number of bacteria. Few of the semen and prostatic fluid samples were sterile, but the others contained only small numbers of contaminating organisms, mainly saprophytes. Therefore, the samples were used in these experiments without further treatment.

*Blood sera.* Ten cubic centimeters of blood were obtained from each of 7 prostatic fluid donors who had a history of gonorrhea. The blood was allowed to clot, the serum removed and stored in the deep freeze at −15 degrees F.

*Organisms and test media.* The organisms used, their sources, and the media used can best be presented in tabular form (Table I).

## METHODS

*Antibacterial tests.* The technique used to test the antibacterial activity of the secretions was the Oxford cup method as described by Kolmer. Pour plates of the organism were made by placing 0.1 cubic centimeter of a 24 hour broth culture in 100 cubic centimeters of melted agar. Thirteen cubic centimeters of the mixture were dispensed into each Petri dish. The agar plates were allowed to cool and placed in the refrigerator until used.

The cylinders were stainless steel cups 8 millimeters in diameter. These were sterilized by autoclaving and dry heat at 300 degrees F. and subsequently placed on the agar pour plates using aseptic technique. After the cups were allowed to "set" on the agar for a period of time, 3 to 5 drops of the test solution were placed in each cup.

The plates were then covered with sterile porcelain covers and incubated at 37 degrees

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C. for 24 hours. After this period, the diameters of the areas of growth inhibition (the inner clear zone) around the cups were measured with a pair of dividers. One cylinder on each plate was used for a penicillin test solution of 2 units per milliliter.

*Heat inactivation.* One-half cubic centimeter amounts of semen and/or prostatic fluid were heated in a water bath at different temperatures for varying periods of time. After heating, the solutions were allowed to cool and then tested for antibacterial activity.

*Dialysis.* In one test, approximately 2 cubic centimeters of semen or prostatic fluid (½ c.c. amounts in subsequent tests) were placed in cellophane tubing for dialysis. The bags were then placed in 5 cubic centimeters of sterile distilled water. The whole system was placed in a mechanical shaker in the warm room (37 degrees C.) for 2 hours and then in the refrigerator. Several changes of distilled water were made over a 24 hour period and all the dispersion fluids combined. In the first test this amounted to 45 cubic centimeters of fluid, but in the two subsequent tests this totaled 20 cubic centimeters. This material and the portion remaining in the cellophane sac (about 3 c.c. in the first test and 1 c.c. in the next 2 tests) were separately tested for antibacterial activity with Staphylococcus aureus F and Staphylococcus aureus L.

*Calcium precipitation.* Two hundred milligrams of sodium citrate were added to 100 cubic centimeters of melted agar containing the test organisms and pour plates made according to the usual method. Various semen and prostatic fluid specimens were tested on these pour plates to detect any change in their antibacterial activity in the presence of this calcium precipitating agent.

Sodium citrate was added to some samples and the supernatant fluids tested to determine any change in antibacterial activity against the various organisms.

*Extraction.* Eighteen samples of semen and prostatic fluid were pooled to make up 8 cubic centimeters of test material. One cubic centimeter was put aside for comparison with the material obtained from the extraction.

Twenty-one cubic centimeters of 50 per cent aqueous alcohol, adjusted to *p*H 2.22 by addition of dilute hydrochloric acid, were added to 7 cubic centimeters of the test material. The mixture was shaken often at room temperature (28 degrees C.) for an hour to allow for extraction.

The acid-alcohol-semen-prostatic fluid mixture was centrifuged at 2,000 revolutions per minute for 20 minutes, the supernatant of 25 cubic centimeters volume removed, and the residue discarded. Two volumes (50 c.c.) of cold acetone were added to the supernatant fluid and a heavy white precipitate formed.

The precipitate was recovered by centrifugation, washed twice with cold acetone, and then allowed to dry overnight at 28 degrees C. The precipitate was dissolved in 8 cubic centimeters of sterile triple-distilled water and tests for antibacterial activity were made using Staphylococcus aureus G and Micrococcus lysodeikticus. The aliquot set aside before ex-

TABLE I.—ORGANISMS TESTED, THEIR SOURCES, AND MEDIA USED FOR TESTS ON EACH

| Organism used | Penicillin sensitivity (2 units/ml.) | Source | Media used |
|---|---|---|---|
| Staph. aureus F | Sensitive 23 mm. zone | Recently isolated from leg ulcer | Beef extract agar |
| Staph. aureus G | Sensitive 24 mm. zone | Recently isolated from throat | Beef extract agar |
| Staph. aureus L | Not sensitive | Stock culture | Beef extract agar |
| Staph. aureus P | Not sensitive | Recently isolated from throat | Beef extract agar |
| Staph. aureus X | Sensitive 21 mm. zone | Isolated from patient's prostatic secretion (prostatic abscesses) | Beef extract agar |
| Staph. aureus $X_1$ | Sensitive 25 mm. zone | Isolated from same patient's prostatic fluid (1 mo. later) | Beef extract agar |
| Esch. coli | Not sensitive | Stock culture | Beef extract agar |
| N. gonorrhoeae | Sensitive 35 mm. zone | Stock culture | Trypticase soy agar, Mueller-Hinton agar |
| N. meningitidis | Sensitive 24 mm. zone | Stock culture | Trypticase soy agar, Mueller-Hinton agar |
| Str. hemolyticus | Sensitive 20 mm. zone | Stock culture | *Blood agar, trypticase soy agar |
| B. cereus | Sensitive 30 mm. zone | Standard strain used for antibiotic titrations | Beef extract agar |
| M. lysodeikticus | Sensitive 10 mm. zone | Stock culture | Douglas' agar |

*8 semen specimens tested on blood agar.
10 semen specimens tested on trypticase soy agar.
10 prostatic fluid specimens tested on trypticase soy agar.

TABLE II.—THE INHIBITORY ACTIVITY OF HUMAN SEMEN SPECIMENS AGAINST VARIOUS BACTERIA*

| Test organism | No. showing inhibition/No. tested | Zone of inhibition (diameters in mm.) | |
|---|---|---|---|
| | | Range | Average |
| Staph. aureus F | 17/18 (94%) | 7.9–13.8 | 11.26 |
| Staph. aureus G | 18/20 (90%) | 9.1–15.1 | 11.76 |
| Staph. aureus L | 19/20 (95%) | 8.9–15.1 | 12.27 |
| Staph. aureus P | 16/18 (89%) | 9.9–16.0 | 12.25 |
| Staph. aureus X | 5/8 | 9.0–12.1 | 11.42 |
| Staph. aureus $X_1$ | 3/5 | 9.9–12.8 | 11.30 |
| Esch. coli | 10/15 (67%) | 8.8–12.2 | 10.03 |
| N. gonorrhoeae | 9/11 (82%) | 8.8–9.9 | 9.26 |
| B. cereus | 20/20 (100%) | 8.4–16.2 | 11.90 |
| Str. hemolyticus | 0/18 | — | — |
| N. meningitidis | 6/8 | 7.7–8.2 | 7.95** |
| M. lysodeikticus | 3/3 | 11.9–14.3 | 12.73 |

*Samples from 19 donors.
**Semen specimens frozen and thawed several times.

traction and the extracted material at full strength and at dilutions of ½, ¼, ⅛, and 1/16 were assayed for antibacterial activity.

## RESULTS

### *Antibacterial Activity of Semen and Prostatic Fluid*

These experiments showed that semen and prostatic fluid had an antibacterial activity against a variety of organisms. Twenty-two semen specimens were obtained from 19 individuals and 109 prostatic fluid samples from 50 individuals.

Table II presents the data on the inhibitory action of human semen. The width of the zones of inhibition is given for the various organisms tested. As shown, 89 to 95 per cent of the specimens tested showed activity against Staphylococcus aureus strains F, G, L, and P, whereas, Staphylococcus aureus X and $X_1$ strains were inhibited only by about 60 per cent of the samples tested. These latter two organisms had been isolated from a prostatic infection.

The Staphylococcus aureus strains were inhibited by the semen to an average zone diameter of approximately 12 millimeters. Two units of penicillin per milliliter inhibited the sensitive strains to an average zone width of 23 to 24 millimeters. A comparison of the inhibition zones of semen and the penicillin control shows that semen produces a zone approximately ½ as large in diameter and ¼ as large in area as that given by the penicillin control. The penicillin-resistant organisms Staphylococcus aureus L and P, were as susceptible to the action of seminal fluid as were the penicillin-sensitive strains.

Escherichia coli was susceptible to the antibacterial activity of semen in fewer instances than the strains of Staphylococcus aureus tested. Neisseria gonorrhoeae, Bacillus cereus, Neisseria meningitidis, and Micrococcus lysodeikticus were susceptible to the inhibitory activity of human semen, but Streptococcus hemolyticus was unaffected by every specimen tested.

The results of tests with prostatic fluids are summarized in Table III. The results obtained with prostatic fluid were similar to those observed with semen. Staphylococcus aureus, Escherichia coli, Bacillus cereus, and Micrococcus lysodeikticus were inhibited to a similar extent. The Staphylococcus aureus X strains again were inhibited by fewer of the specimens than the other strains of staphylococci. As with semen, Streptococcus hemolyticus was unaffected by the antibacterial action of the prostatic fluids tested.

However, with the Neisserian organisms, there was a difference in the activity of the fluids. With Neisseria meningitidis, semen inhibited the organism in 6 out of 8 samples tested to an average zone of 7.95 millimeters, but these specimens, as indicated, were frozen and thawed several times. This manipulation probably decreased the potency of the antibacterial factor. The prostatic fluid samples which were not repeatedly frozen and thawed inhibited Neisseria meningitidis in 10 out of 12 cases with an average inhibition zone diameter of 13.85 millimeters.

It was noted further that semen inhibited Neisseria gonorrhoeae in 9 out of 11 specimens tested with an average zone diameter of 9.26 millimeters, and that with prostatic fluids 37 out of 39 samples showed inhibitory activity. However, the inhibition zones obtained with prostatic fluids could be divided into two groups. Twenty-nine samples in-

hibited this organism with zones averaging 8.57 millimeters in diameter, comparable to the zones obtained with semen specimens. In contrast, the other 8 samples from 4 individuals, 3 of whom had histories of gonorrhea, gave inhibition-zone widths averaging 27.02 millimeters, indicating that they had the greatest activity observed in these experiments.

Blood serum specimens from 7 prostatic fluid donors with histories of gonorrhea were tested in Oxford cups on pour plates of Neisseria gonorrhoeae along with control sera from individuals with negative histories. The normal serum and 5 of the test sera inhibited Neisseria gonorrhoeae to a slight degree (8 to 9 mm. zone diameter). Two of the test sera, which were obtained from 2 of the 4 individuals whose prostatic fluid showed marked inhibition, showed larger zones of inhibition (15.0 mm. zone diameters). On the other hand, serum from 1 of the 4 individuals, whose prostatic fluid displayed marked antigonococcal activity, had no greater activity against the gonococcus than did normal serum.

All the sera from the individuals with positive histories of gonorrhea gave negative results with the gonococcal complement fixation test.

### *Properties of the Antibacterial Agent in Semen and Prostatic Fluid*

*Effect of heat.* With the limited number of samples tested it was seen that the factor in semen and prostatic fluid that inhibits Staphylococcus aureus is heat stable, resisting heating at 100 degrees C. for up to 30 minutes, whereas the antibacterial factor for Micrococcus lysodeikticus in these two secretions was reduced in activity by mild heat treatment and inactivated after 100 degrees C. for 10 minutes. Table IV shows the results of these heat experiments.

*Effect of dialysis.* These experiments demonstrated that the inhibitory factor in semen and prostatic fluid passed through cellophane dialyzing membranes. This factor, therefore, was a material in true suspension and of a small molecular size. Table V lists these results.

TABLE III.—THE INHIBITORY ACTIVITY OF HUMAN PROSTATIC FLUID SAMPLES AGAINST VARIOUS BACTERIA*

| Test organism | No. showing inhibition/No. tested | Zone of inhibition (diameters in mm.) | |
|---|---|---|---|
| | | Range | Average |
| Staph. aureus G | 47/51 (92%) | 7.8–20.9 | 12.14 |
| Staph. aureus L | 34/37 (92%) | 8.1–15.1 | 11.22 |
| Staph. aureus X | 9/14 (64%) | 9.6–14.2 | 12.20 |
| Staph. aureus $X_1$ | 1/1 | 11.80 | 11.80 |
| Esch. coli | 29/47 (62%) | 7.8–13.5 | 9.67 |
| N. gonorrhoeae | 29/31 (94%)<br>8/8 (100%) | 8.1–11.1<br>15.8–39.0 | 8.57<br>27.02 |
| B. cereus | 15/16 (94%) | 8.7–18.2 | 12.46 |
| Str. hemolyticus | 0/10 | — | — |
| N. meningitidis | 10/12 (83%) | 8.2–19.0 | 13.85 |
| M. lysodeikticus | 2/2 | 12.0–17.1 | 14.55 |

*Samples from 50 donors.

*Effect of calcium precipitation.* The precipitation of calcium ions from the secretions either by addition of sodium citrate to the culture medium or by direct addition to the specimens had no appreciable effect upon the inhibitory activity of semen and prostatic fluid.

*Effect of extraction with acid alcohol.* An antibacterial factor was extracted from seminal fluid by this method. However, this factor had its inhibitory activity on Micrococcus lysodeikticus but not on Staphylococcus aureus. A 1/16 dilution of the solution of the dry precipitate in 8 cubic centimeters of distilled water to adjust to its original volume gave a large zone of inhibition (13.8 mm.), indicating that the extraction resulted in concentration of the lysozyme-like factor present.

## DISCUSSION

The inhibition of various strains of bacteria by human serum and prostatic fluid is similar to that reported by Youmans and his associates with prostatic fluid from dogs. They found that Staphylococcus aureus and Escherichia coli were inhibited by dog prostatic secretions and that Neisseria gonorrhoeae was slightly susceptible to the inhibitory factor in this fluid. In the present study, it was found that Staphylococcus aureus, Escherichia coli, and Neisseria gonorrhoeae were inhibited by

TABLE IV.—EFFECT OF HEAT ON ANTIBACTERIAL ACTIVITY OF SEMEN AND PROSTATIC FLUID

| Test organism | No. of tests | Heating | | Inhibition zones (diameters in mm.) |
|---|---|---|---|---|
| | | Temp. °C. | Time, min. | |
| Staph. aureus G | 9 | Unheated | | 11.64 aver. |
| | 1 | 70 | 10 | 14.80 |
| | 1 | 70 | 20 | 14.20 |
| | 5 | 70 | 30 | 13.22 aver. |
| | 1 | 75 | 10 | 13.70 |
| | 1 | 75 | 20 | 14.20 |
| | 1 | 75 | 30 | 14.10 |
| | 4 | 75 | 60 | 11.00 aver. |
| Staph. aureus L | 7 | Unheated | | 10.50 aver. |
| | 4 | 70 | 30 | 12.40 |
| | 1 | 100 | 20 | 10.20 |
| | 1 | 100 | 30 | 11.00 |
| | 1 | 100 | 40 | 0 |
| M. lysodeikticus | 4 | Unheated | | 17.30 aver. |
| | 1 | 70 | 10 | 8.50 |
| | 1 | 70 | 20 | 8.20 |
| | 1 | 70 | 30 | 7.80 |
| | 1 | 75 | 10 | 7.60 |
| | 1 | 75 | 20 | 7.60 |
| | 1 | 75 | 30 | 7.50 |
| | 1 | 100 | 10 | 0 |
| | 1 | 100 | 20 | 0 |
| | 1 | 100 | 30 | 0 |

human seminal fluid and prostatic fluid, but that Streptococcus hemolyticus was not susceptible to their inhibitory action, whereas it had been reported as susceptible to the antibacterial activity of dog prostatic fluid by Youmans and his associates.

Rozansky and his associates, using the Oxford cup technique, found that 3 strains of Staphylococcus aureus were inhibited by human semen, but that the Escherichia coli strains tested were not susceptible to the inhibitory factor. In the observations here recorded, 6 strains of Staphylococcus aureus and a strain of Escherichia coli were inhibited by semen and prostatic fluid, but Escherichia coli was less susceptible to this inhibitory action. In addition to these organisms, Neisseria gonorrhoeae, Bacillus cereus, Neisseria meningitidis, and Micrococcus lysodeikticus were also found to be sensitive to the inhibitory factor of seminal fluid and prostatic secretion.

Bacillus cereus, a saprophytic organism, was used as a control strain in these experiments since its sensitivity to a wide variety of antibiotics has led to its use for assay of their potency by the same technique used here to study the antibacterial activity of seminal and prostatic fluids. It has served, therefore, as a point of reference for evaluation of the inhibitory activity of these fluids, and Tables II and III show average diameters of inhibition zones of 11.9 and 12.46 millimeters with these fluids as compared with a zone diameter of 30 millimeters obtained with 2 units of penicillin per milliliter.

The purpose of the penicillin control was threefold. By checking every pour plate with a known penicillin control solution, the penicillin sensitivity of the organism could be ascertained and checked to see if it remained approximately the same from test to test. Secondly, the zone width of the penicillin control gave the investigators information concerning the correct seeding of the pour plate. Lastly, the penicillin control served as a reference against which the inhibition zone diameters of the test solutions could be compared.

With Staphylococcus aureus the inhibitory factor in seminal fluid and prostatic secretions produced an inhibitory zone diameter ½ as large and an inhibitory zone area ¼ as large as 2 units of penicillin per milliliter. It can be seen that the range of activity of the antibacterial factor in semen and prostatic fluid compares favorably with the action of 2 units of penicillin per milliliter, which is more than twice the concentration usually considered of therapeutic significance.

Two Staphylococcus aureus strains, X and $X_1$, were isolated from prostatic fluids. These organisms were susceptible to the inhibitory action of seminal fluid and prostatic secretions in only 60 per cent of the cases, whereas the other strains were inhibited in 89 to 95 per cent of the samples studied. These two strains seem to be more resistant to the test fluids and they may have become so while they were active as agents in a prostatic infection.

In one instance, it was possible to study the change in the antibacterial activity of an in-

dividual's prostatic fluid during the course of a prostatic infection. This patient was the one from whom the Staphylococcus aureus X was isolated. A sample of prostatic fluid obtained at the onset of the infection was normal in inhibitory activity against this organism. However, 2 samples of prostatic fluid obtained during the height of the infection demonstrated little activity against this organism. Two samples obtained during the period of improvement demonstrated some activity against the staphylococcus, whereas a sample obtained after the infection had entirely cleared exhibited normal activity against this organism. The antibacterial activity against Staphylococcus aureus X, the infective agent, disappeared during the height of infection, but reappeared during convalescence and regained full activity on recovery. The correlation of the status of the infection with the presence or absence of antibacterial activity in the prostatic fluid suggests that this factor plays an important role in prostatic infections.

Neisseria gonorrhoeae was only slightly susceptible to the action of semen and prostatic fluid in most instances. However, in 4 cases the inhibition zones attained were markedly larger. Three of these 4 individuals had histories of gonorrhea. The past history in the fourth case was undetermined.

Tests with sera from these 4 individuals by the method described showed that in 2 cases increased inhibition occurred which could have been due to the presence of specific antibody in the serum. The serum antibody might diffuse into the seminal fluids, thus accounting for their inhibitory activity. However, all of these sera gave negative results in the gonococcal complement fixation test indicating that the usually detectable serum antibody for this organism was absent. Of course, one could postulate the presence of other types of antibodies for the gonococcus in these sera.

Micrococcus lysodeikticus was inhibited by semen and prostatic fluid in the few cases studied. It is interesting to note that the factor responsible for this inhibition was partially inactivated at temperatures of 70 degrees C. and 75 degrees C. for varying periods of time and destroyed by 100 degrees C. for 10 minutes. The factor that inhibits Staphylococcus aureus was not destroyed at this temperature. It resisted 100 degrees C. for 30 minutes. This indicates that there are two factors responsible for the inhibitory activity of semen and prostatic fluid. One factor is lysozyme-like, active against Micrococcus lysodeikticus mainly and diminished in activity after heating at 70 to 75 degrees C. and inactivated completely after heating at 100 degrees C. for 10 minutes. The other factor has inhibitory activity against pathogenic bacteria such as Staphylococcus aureus, Escherichia coli, Neisseria meningitidis, and Neisseria gonorrhoeae, which are not susceptible to lysozyme or lysozyme-like factors. It is much more heat stable than the lysozyme or lysozyme-like factor, resisting a temperature of 100 degrees C. for 30 minutes. In recent studies, Gurevitch and his associates have presented evidence that this heat-stable activity might be due to spermine present in semen.

TABLE V.—EFFECT OF DIALYSIS ON THE ANTIBACTERIAL ACTIVITY OF SEMINAL FLUID

| Sample | Amount c.c. | Inhibition zones for Staph. aureus G (Diameters in mm.) | | |
|---|---|---|---|---|
| | | Before dialysis | Sac contents* | Dispersion fluid** |
| 1 | 2 | 12.1 | 8.9 | 9.0 |
| 2 | ½ | 11.2 | 8.4 | 12.9 |
| 3 | ½ | 11.7 | 8.0 | 10.1 |

*Inhibition of Staph. aureus G by cellophane sac contents after dialysis.
**Dialysis dispersion fluid concentrated to ½ c.c.

The acid-alcohol extraction further suggests the presence of two factors. The factor that inhibits Staphylococcus aureus was not extracted by this method, whereas the lysozyme factor was.

The inhibitory factors are present in the fluid portion of the semen because specimens with low sperm content or no sperm at all inhibited the test organisms as efficiently as did normal specimens. Furthermore, there are usually few if any sperm in prostatic fluids, so their ability to inhibit the various test organisms gives further evidence that the inhibitory factors were in the fluid part of the seminal material.

The possibility exists that the leucocytes that occur in prostatic fluids and semen, particularly pathological specimens, may be re-

sponsible for the lysozyme-like activity of these fluids against Micrococcus lysodeikticus. Bradford and Roberts showed that leucocytes have such lysozymic activity. However, normal specimens containing few leucocytes inhibited Micrococcus lysodeikticus equally as well as the pathological specimens. It appears that the lysozyme-like factor is present in semen and prostatic fluid as such and is not due to their content of leucocytes.

The factors in semen and prostatic fluid probably aid in the defense of the male genitourinary tract against pathogenic bacteria, but may also play another role. Matthews and Buxton found in cultures of the cervix in the female Escherichia coli, Streptococcus viridans and Streptococcus hemolyticus strains that were highly spermicidal. Other organisms such as diphtheroids, streptococci, and hemolytic and nonhemolytic staphylococci were entirely innocuous to spermatozoa. Semen and prostatic fluid had an inhibitory effect on Escherichia coli. Therefore, the antibacterial properties of these fluids may protect spermatozoa in the vagina from the spermicidal action of this organism.

SUMMARY

There appear to be two antibacterial factors in human semen and prostatic fluid. One of these factors is heat stable, resisting temperatures up to 100 degrees C. for 30 minutes, and it is not extracted from test material by acid alcohol. It possesses antibacterial activity for Staphylococcus aureus, Escherichia coli, Neisseria gonorrhoeae, Neisseria meningitidis, and Bacillus cereus.

The other factor in human semen and prostatic fluid is relatively heat labile, being completely inactivated at 100 degrees C. for 10 minutes. It is extracted from semen and prostatic fluid by acid-alcohol and its primary inhibitory action is against Micrococcus lysodeikticus. This factor is lysozyme or a lysozyme-like substance.

Preliminary observations suggest that this inhibitory activity of semen may be important in genitourinary infections such as prostatitis due to Staphylococcus aureus and gonococcal infections.

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# VARIATIONS IN THE FORMATION AND VASCULAR RELATIONSHIPS OF THE BILE DUCTS

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PERUSAL of the available literature has revealed a lack of accurate information on the relationships of the hepatic ducts to the accompanying hepatic arteries and portal vein in the intrahilar area and immediately upon emerging from the liver. These relationships assume clinical importance in the re-establishment of the flow of bile to the intestine following trauma to the ducts, in inflammatory processes, and in resection for neoplasms. In many instances, where direct end-to-end anastomosis of severed duct ends is impossible, the remaining stump of the hepatic duct must be sought and joined to the intestinal tract. Meager, indeed, are references to anatomical landmarks which might be of aid in locating the hepatic duct stump in a dissection rendered difficult by the scar tissue of preceding operations or disease processes. Until recently the only described method for locating such a duct was that dependent on aspiration for bile in the hilar area. Cole, Reynolds, and Irenius[1] (1949) have discussed the relationship of the hepatic ducts to the portal vein and use this vessel as an aid in locating the remnant of the duct.

The current investigation was undertaken in order to establish the relationships of the hepatic ducts to the variable blood vessels and to the lesser lobes and the sulci on the inferior surface of the liver.

## Materials and Methods

Detailed dissections of structures in the hepatoduodenal ligament and in the hepatic porta were carried out in 35 consecutive specimens in the laboratory of gross anatomy of Northwestern University Medical School. In respect to the general anatomy of the hepatic pedicle, these new observations supplement earlier series reported by Lyman, Lander and Anson (1941), and by Daseler, Anson, Hambley, and Reimann (1947).

Data were recorded on a prepared form, and 35 millimeter color photographs were taken of each specimen. Permanent records were thus obtained quickly and accurately for use in subsequent detailed study of the area. Drawings of the important variations or relationships were made from the specimens with the aid of the photographs.

Variations of the gallbladder, the cystic and common bile ducts, and the origin of the hepatic arteries, although not the primary object of the investigation, were, nevertheless, recorded and will be presented for the purpose of comparison and addition to the existing literature.[2]

## Observations and Discussions

### Bile Ducts

Major variations in the gallbladder and biliary ducts are much less common than those found in the accompanying arterial patterns. Eisendrath is quoted by Mentzer

Contribution No. 583 from the Anatomical Laboratory of Northwestern University Medical School.

[1]For papers published in coauthorship, to which frequent reference is required in the text, the names of the senior author's colleagues and the year of publication will be omitted after initial citation has been made.

[2]The early works in this field include the accounts by Descomps (1910) and Rio Branco (1912) on the blood vessels, and Ruge (1908), Descops and Kunze (1911) on the biliary passages. Eisendrath's several papers (1918–1920) summarized and reviewed these earlier investigations. Thompson (1933) carried out a series of dissections and presented an exhaustive review and statistical compilation of the literature. Since that time numerous studies of the biliary region have been published, notable among which are those of Browne (1940), and Daseler and coauthors. Boyden (1926) investigated anomalies of the biliary ducts in an exceptionally valuable study, based upon their comparative and embryological significance. Gross (1936) reviewed 148 cases of congenital anomalies of the gallbladder, while Schachner (1916) was one of the few workers who commented on those variations on the inferior surface of the liver which accompany anomalous locations of the gallbladder. Surgical articles on operative injuries to the biliary structures and predisposing anatomical variations include those of Kehr (1913), Eisendrath (1920), Jacobson (1916), Eliot (1918), McWhorter (1923), Flint (1922–1923), Jackson (1938), Browne (1940), and the recent article by Cole and associates.

TABLE I.—LENGTHS OF COMMON BILE DUCT IN RELATION TO TYPE OF CYSTOHEPATIC JUNCTION

| | No. of specimens | Total per cent | Before separation cm. | After separation cm. |
|---|---|---|---|---|
| Common bile duct excluding parallel junctions | 27 | 79.4 | 6.6 | No difference |
| Common bile duct in parallel junctions | 7 | 21.6 | 6.6 | 4.0 |
| Combined common bile duct | 34 | 100.0 | 6.6 | 6.1 |

(1929) in stating that anomalous bile ducts are found in approximately 8 per cent of routine necropsies. The recent study of Michels (1951) on 200 specimens revealed accessory ducts in 18 per cent.[1]

*Common bile duct.* This is the least variable segment of the biliary duct system; usually it departs from the anatomic norm only in respect to such features as length, vascular relationships, and juncture with the pancreatic duct.[2]

The length of the common bile duct varied with the overall body size, the level of the duodenum, and the point at which the cystic duct joined the common hepatic duct. As might be expected, the range was great. Brewer (1900) and Lander and his associates, reported extremes of 3.7 to 11.9 centimeters and 2.0 to 9.5 centimeters, respectively, and averages of 7.7 and 4.9 centimeters. McWhorter (1923) found an average length (20 cases) of 6.24 centimeters.

In any such measurement studies, the results are of little value unless the methods and points of reference are clearly outlined to the reader or future investigator. Statistics on the length of the common bile duct as well as those on the length of the common hepatic and cystic ducts are directly affected by the recognition and careful dissection of the long and short parallel types of junction between the latter two ducts (Figs. 1b and 1c). For example, separation of a 4 centimeter parallel course will add that length to the common hepatic and cystic ducts, and subtract the same amount from the length of the common duct. In Table I are recorded the differences in the average measurements of the common bile duct as affected by this parallelism.

The absence of the supraduodenal portion of the common bile duct, due to a prolonged parallel course of the cystic duct, has been described by several writers. Flint reported 28 examples (14 per cent) of such absence in his study of 200 bodies, while Thompson listed 109 instances in reports covering 421 dissections (23 per cent). The present authors found 7 examples of this type in 35 specimens (incidence, 20 per cent).

The vascular relationships of the common bile duct described in the literature include many cases of anterior crossing of the gastroduodenal, common hepatic, right hepatic, and so-called supraduodenal arteries. Thompson reported the presence of ventral relationships in 31 of his 50 specimens. This variation is of interest to the surgeon carrying out an exploration of this portion of the common duct. For many years the opinion was held by anatomists and surgeons alike that there existed no ventral arterial relationships, and hence no hazard of arterial injury in carrying out exploration of the common duct.

The supraduodenal artery deserves special mention in that it is omitted in many anatomical texts, and there is confusion in the literature concerning its incidence and exact nature. Brewer first described a small vessel which arose most commonly from the gastroduodenal artery, crossed the common bile ventrally in many cases, and seemed to send branches to the first part of the duodenum and structures within the distal portion of the hepatoduodenal ligament. Wilke (1911) again described this vessel, and termed it the supraduodenal artery. Varying statistics on the incidence of such an artery have been recorded, Browne reporting 56 examples in 280 bodies studied (44.6 per cent of which

[1]Professor Michels' detailed study of the arterial supply of the supramesocolic viscera is based upon painstaking dissections of 200 cadavers; his careful drawings served as bases for the statistical results recorded in his article. The report is a classical contribution which is invaluable alike to the anatomist and the surgeon. B.J.A.

[2]The latter will not be considered here. Reports of congenital absence are very confusing and many reported cases are actually atresias of undetermined etiology. Kehr reported 8 cases of reduplication and Courvoisier 1 case. The latter's case had one duct draining to the duodenum and one to the transverse colon. Two cases of termination of a single common duct in the stomach are cited by Mentzer. Examples of these rare anomalies cannot be expected in a small series; significantly, they were not found in the 500 specimens studied earlier at this institution (6).

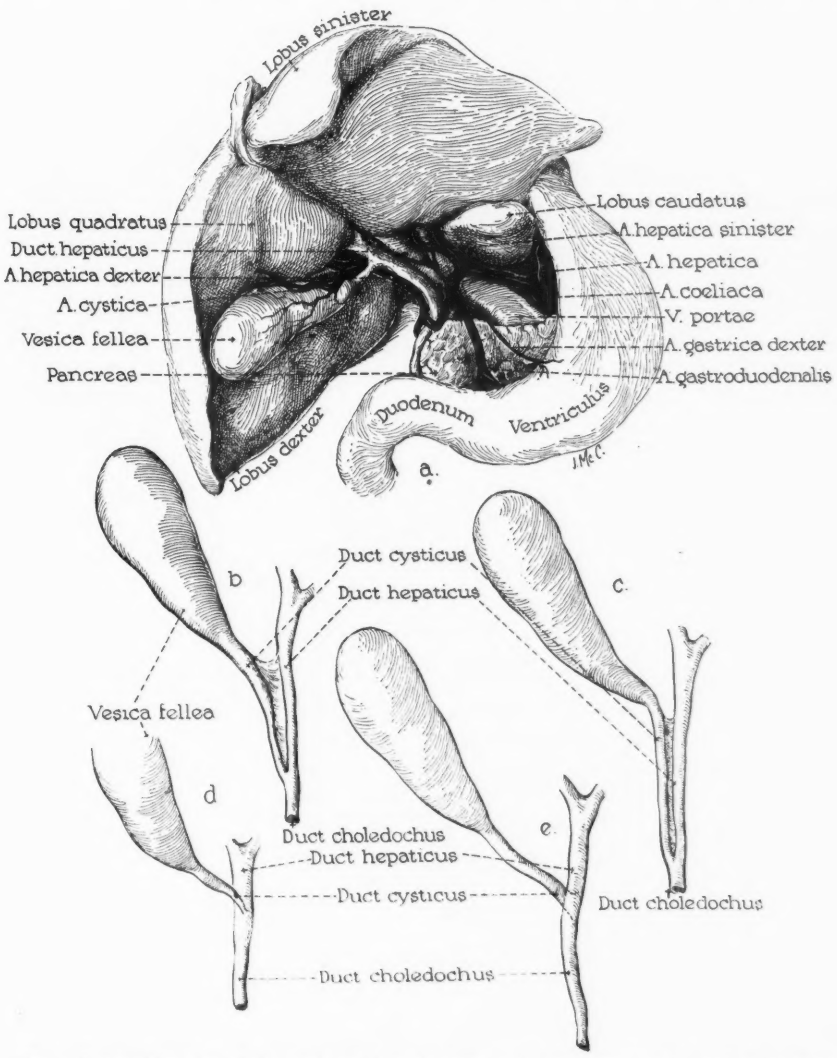


Fig. 1. Types of junction of the cystic and hepatic ducts. a, Normal acute angle junction. b, Short parallel type of junction. c, Long parallel junction. d, Anterior spiral junction. e, Posterior spiral junction.

vessels coursed anterior to the common bile duct). The present authors found only 4 small arterial branches with the described distribution (11.4 per cent). Special injection methods, as used by Wilke, are necessary for accurate study of arterial branches of such slight caliber.

There occurs another arterial branch which crosses the anterior aspect of the common bile duct with great regularity; this is the posterior superior pancreaticoduodenal artery, described in several recent anatomical studies of the arterial supply of the pancreas and duodenum, including that of Pierson.

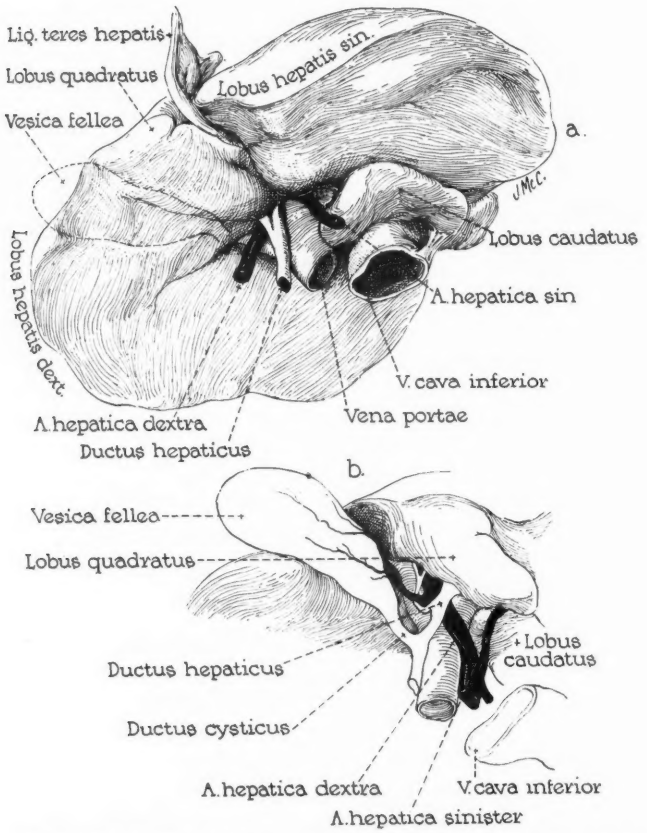


Fig. 2. Relationship of the emerging hepatic ducts to the quadrate lobe of the liver. a, Normal arrangement (88 per cent of specimens). b, Second most common arrangement (12 per cent) in which the hepatic ducts emerge closer to the gallbladder fossa than to the "apex" of the quadrate lobe. Noteworthy is the accessory hepatic duct which curves posterior to the cystic artery.

Pierson found this artery present in 96 per cent of his specimens and quoted Petran in stating that this vessel crosses anterior to the common bile duct in 86 per cent.[1]

The posterior superior pancreaticoduodenal artery usually arises from the gastroduodenal artery just as the latter vessel disappears posterior to the duodenum (Fig. 3b). The posterior and anterior superior pancreaticoduodenal arteries may arise from a common stem, but the latter artery more often takes origin at a lower level, from the gastroduodenal. The former vessel courses lateralward across the anterior aspect of the common bile duct to reach the sulcus between the duodenum and pancreas on their posterior surfaces, often forming an arterial loop about the terminal end of the duct. It then runs downward to anastomose with a posterior inferior pancreaticoduodenal branch from either the superior mesenteric or one of the upper intestinal branches.

[1]In a current study of pancreaticoduodenal arteries, carried out in the laboratory at Northwestern University Medical School, this same relationship obtained in the great majority of specimens. The artery may well be that which some authors have included in the category of supraduodenal artery.

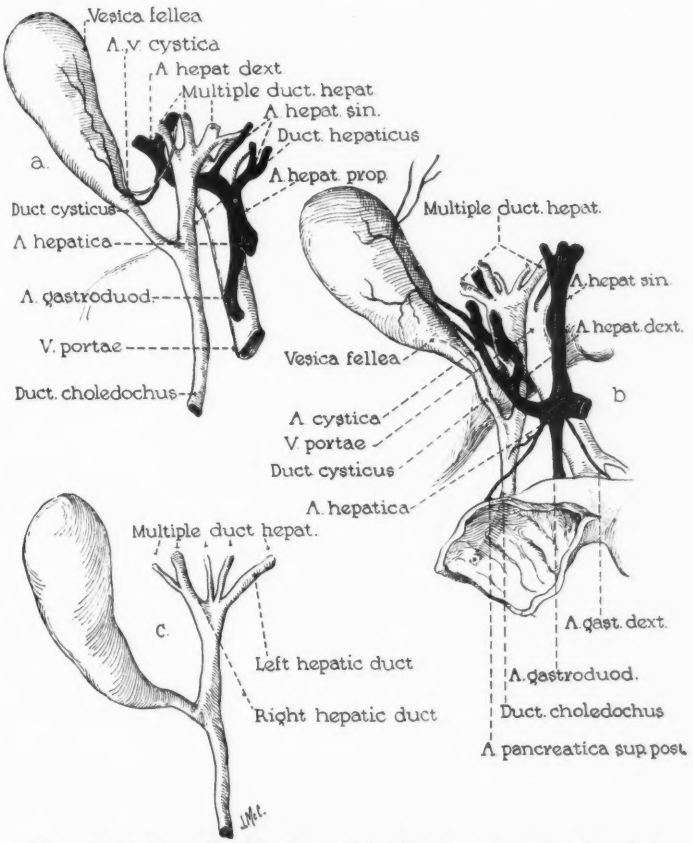


**Fig. 3. Multiplicity of hepatic ducts which join to form the common hepatic duct. From 10 intrahilar dissections. a, Single "middle" hepatic duct (4 specimens). b, Paired hepatic ducts of moderate size, which join the point of juncture of the right and left hepatic ducts. The large hepatic duct which skirts the right hepatic artery rejoins the common hepatic duct. c, Schematic representation of the intrahilar ducts present in specimen depicted in Figure 3b.**

The present authors found 33 examples of a posterior superior pancreaticoduodenal artery, arising with a single exception from the gastroduodenal artery. The exceptional source was an accessory right hepatic artery. All others (32) crossed anterior to the common bile duct; 28 of the 32 (87.5 per cent) lay at retroduodenal level, while 4 (12.5 per cent) crossed anterior to the supraduodenal portion of the duct (Fig. 3b).

Other vessels encountered in the present series which coursed anterior to the supraduodenal portion of the common duct were the gastroduodenal artery in 2 instances (5.7 per cent), and the common hepatic artery[1] in 1 instance (2.9 per cent). Previous investigators have found a much higher incidence of the

[1]The entire hepatic artery from its point of origin at the celiac axis to its division into right and left hepatic rami is referred to as *a. hepatic propria* in the BNA terminology. Some authors have used the name common hepatic artery to designate this same segment and have employed the term hepatic artery proper to describe that portion of the vessel from the gastroduodenal to the point of division into the hepatic rami. In the accompanying text the first portion of the vessel is named hepatic proper, while the succeeding segment, from the point of origin of the gastroduodenal to that at which the segment divides into right and left rami, is named common hepatic (since it is the "common" source of vessels to the lobes of the liver). In labelling the figures the standard BNA terms are used. E.V.J.

TABLE II.—LENGTH OF COMMON HEPATIC DUCT IN RELATION TO TYPE OF CYSTIC-HEPATIC DUCT JUNCTION

| | No. of specimens | Total per cent | Before separation cm. | After separation cm. |
|---|---|---|---|---|
| Common hepatic ducts, excluding parallel cystic-hepatic junctions | 26 | 78.8 | 2.9 | No difference |
| Common hepatic ducts in parallel type junctions | 7 | 21.2 | 2.9 | 5.2 |
| Combined common hepatic duct figures | 33 | 100.0 | 2.9 | 3.4 |

former relationship (Browne, 27.6 per cent; Thompson, 50 per cent), but they have included retroduodenal as well as supraduodenal relationships. Also reported in the literature as passing anterior to the common bile duct are the right hepatic artery (Browne, 2.1 per cent), the right gastric artery (Thompson, 4 per cent), and the cystic artery (Thompson, 2.3 per cent). In a specimen used for illustration (Fig. 1a), the right hepatic artery crossed anterior to the common bile duct. As a rule, the gastroduodenal artery coursed entirely to the left of the common bile duct, as did the common hepatic artery (Thompson, 93 per cent). The portal vein regularly lay dorsal and partially to the left of the common duct. Cole and his associates express the opinion that the most frequent anterior arterial relationship is the small artery of supply to the common duct which runs on its anterior wall in over 50 per cent of patients seen at operation.

Posterior vascular relationships to the common bile duct are neither as frequent in occurrence nor as important clinically. Thompson concluded that they occurred in approximately 10 per cent of specimens. Vessels crossing behind the common duct include the common hepatic artery (Browne, 0.4 per cent; Daseler and coauthors 1.6 per cent) and the right hepatic artery (Thompson, 8 per cent; Daseler and coauthors 11.6 per cent). Many of the accessory or replacing right hepatic vessels, arising from the superior mesenteric artery, coursed posterior to the portal vein and then crossed or paralleled the lateral or posterolateral aspect of the common bile duct. In the 7 specimens of the present series in which an aberrant right hepatic artery was present, it came into close approximation to the posterolateral aspect of the common bile duct in 6 (Fig. 4b). The remaining anomalous vessel crossed at a higher level. No example of a common or right hepatic artery with posterior relation to the common bile duct was encountered.

*Common hepatic duct.* This duct is of variable length; it is occasionally absent as such when the cystic duct empties at the point of junction of the right and left hepatic ducts, or enters at an even higher level by joining one of the hepatic ducts, more commonly the right. Thompson found 8 examples of the former in 322 specimens, while Daseler and coauthors encountered only a single instance in 500 dissections. In the latter group were found 3 examples of junction of the cystic duct and the right hepatic duct, while Thompson reported only 1 in a total of 100 bodies. A common hepatic duct occurred in 34 (97 per cent) of specimens in the present series.

The question of intrahepatic or extrahepatic formation of the common hepatic duct is a fundamental consideration in the current study. Thompson reported an incidence of 91 per cent for extrahepatic junction of the hepatic ducts in his review of the studies made by previous authors. In the present series such junction occurred in 32 of the 34 specimens (94 per cent) in which the common hepatic duct was present. The exceptions were in cases with markedly enlarged liver, presumably diseased. The statement by Cole and his associates is the exact opposite, there being intrahepatic formation in 90 per cent (seemingly due to the use of the term intrahepatic as synonymous with intrahilar).

Measurements of the common hepatic duct were affected by most of the factors listed as important in the consideration of the common bile duct. The greatest variable was the level at which the cystic duct emptied into the common hepatic duct. McWhorter found the average length in 35 specimens to be 3.0 centimeters. Lander and coauthors reported extremes of 1.0 to 5.0 centimeters with the majority varying between 1.5 and 3.5 centimeters. The present authors' figures are pre-

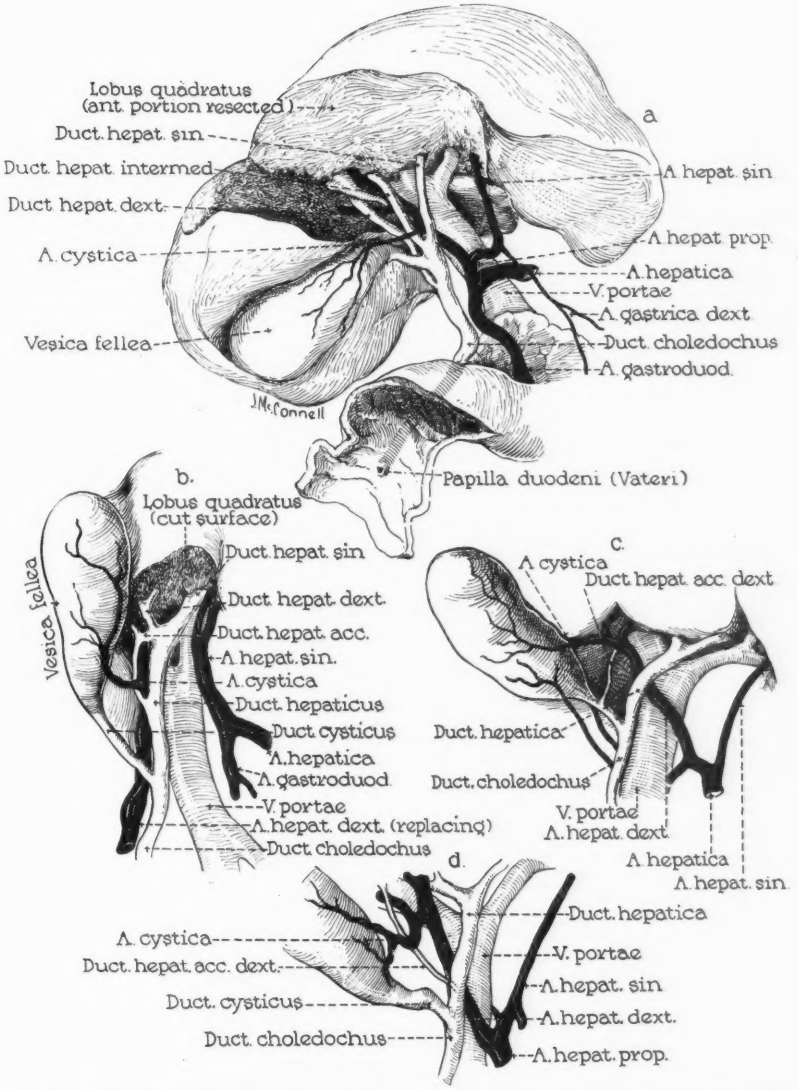


Fig. 4. Extrahilar accessory hepatic ducts. a, Specimen with no common hepatic duct; due to the low insertion of a large right hepatic duct into the common bile duct (i.e., below the cystic duct junction), a common hepatic duct does not exist. The relationship of the cystic artery to the hepatic ducts is also unusual. b, Heretofore undescribed type of accessory hepatic duct (see also Fig. 3b) from the right hepatic duct which coursed around the right hepatic artery and rejoined the common hepatic duct (5 specimens). Also shown is the relationship of an anomalous right hepatic artery to the bile ducts and portal vein. c, Accessory hepatic duct joining the cystic duct (4 specimens). d, Accessory hepatic duct joining the common hepatic duct.

TABLE III.—FREQUENCY OF MODES OF UNION OF CYSTIC AND HEPATIC DUCTS (ON THOMPSON'S CRITERIA)

| Author | No. of specimens | Normal (angular) | | Parallel | | Spiral | |
|---|---|---|---|---|---|---|---|
| | | No. | Per cent | No. | Per cent | No. | Per cent |
| Ruge | 43 | 14 | 33 | 12 | 29 | 16 | 38 |
| Kunze | 39 | 20 | 51 | 19 | 49 | — | — |
| Descomps | 50 | 40 | 80 | 6 | 12 | 4 | 8 |
| Eisendrath | 100 | 75 | 75 | 17 | 17 | 8 | 8 |
| Johnston and Anson | 35 | 22 | 63 | 7 | 20 | 6 | 17 |

sented in Table II, with a record of the differences between the initial gross appearance and that following careful separation of parallel ducts.

In general, the mode was 3 centimeters with 88 per cent falling between 2.0 and 3.5 centimeters (before separation).

*Union of cystic and hepatic ducts.* The cystic duct joins the hepatic duct in a much more variable manner than a reader would be led to believe after a perusal of anatomical textbooks and many of the surgical descriptions. While it is true that the commonly described junction at an acute angle occurs in the majority of bodies, there are regularly encountered variations which, although less frequent, are of equal importance. Ruge did the pioneer work in classifying these variations in three main types. Eisendrath later reviewed and summarized the early reports, emphasizing again the clinical importance of these factors in injury to the biliary duct and in postcholecystectomy syndromes. His tabulation appears in Table III, to which the present authors have appended their results.

1. Angular type. A tabulation of available reports reveals the occurrence of normal or angular insertion (Fig. 1a) in 397 out of 621 specimens (64 per cent). There were 18 examples of definite angular insertion in the present authors' series of 35 specimens (51.4 per cent). In addition, there were 4 specimens for which no accurate classification could be established, the unions falling between angular and posterior (one-quarter turn) spiral types. Inclusion of such specimens with the angular type, as it is assumed previous investigators have done, would bring current percentage to 62.9 per cent.

2. Parallel types. As mentioned earlier, the cystic and common hepatic ducts may run parallel to each other for a varying distance. They are held in intimate contact by firm fibrous tissue, and their point of actual confluence may be indistinguishable on gross inspection. A subdivision of this group into a short parallel type, from 5.0 to 7.0 centimeters in length (Fig. 1b) and a long parallel type, greater than 7.0 centimeters in length (Fig. 1c), has been described by several investigators. A cystic duct of the long parallel type may extend to within 0.5 centimeters of the ampulla of Vater.

Thompson collected 50 examples of the parallel cystic and common hepatic duct which had been subdivided on the basis of parallelism less or greater than 5 centimeters; 60 per cent fell into the category of the short parallel, while 40 per cent were of the long parallel type. Individual reports on the relative frequency of these two types are at wide variance with one another, presumably due to different investigative methods and criteria.

Using Thompson's criteria, the present authors found 7 examples (20 per cent) of short parallel junctions. The longest parallel course was 4 centimeters. These observations suggest that a revised subdivision of these types would do much to emphasize the frequency of parallelism. Classification of ducts with a parallel course shorter than 2 centimeters as belonging to the acute angular type, those from 2 to 4 centimeters as short parallel, and those 4 centimeters and over as long parallel junctions, would more clearly emphasize the second group in which the parallelism begins to be significant. Six of the current specimens (17.1 per cent) would fall into the second group (2 to 3.9 cm.), and only 1 (2.9 per cent) into the third (4 cm.). The average length of parallel course was 2.7 centimeters, the mode was 2.5 centimeters.

3. Spiral types. The cystic duct may wind around the hepatic duct for a quarter-turn, halfway or more, or even through a full turn. The actual point of junction may be on the anterior, posterior, or the medial or left surface of the common hepatic duct. Subdivision

of this group into anterior and posterior spiral types is convenient (Figs. 1d and 1e). Thompson's review lists 67 spiral junctions in 626 reported cases (10.7 per cent), while Eisendrath found 8 in 100 specimens (8 per cent). Other authors have reported widely varying figures on the incidence of this variation. In comparison of anterior and posterior spiral junctions, there were 23 of each type in 46 reported specimens which were so classified. Ruge reported the greatest incidence of spiral junctions (37 per cent); McWhorter and Thompson found the posterior spiral type to be more frequent than the anterior. Lurje (1937) suggested separate grouping of the posterior (quarter turn) insertions and found that this type made up 15.5 per cent of his entire series.

There were 6 examples of spiral insertions in the present authors' lot of specimens (17.1 per cent). Of these, 5 were posterior and 1 was anterior. In addition, 4 specimens presented acute angular junction with insertion toward the posterior surface of the common hepatic duct. Little, if any, parallelism existed in the spiral insertions found in the present group.[1]

From a review of the literature it would appear that the common hepatic and left hepatic arteries course entirely to the left of the common hepatic duct in 96 to 98 per cent of specimens, and that the right hepatic artery crosses posteriorly in approximately 60 to 78 per cent of cases, and anterior to the duct in 12 to 15 per cent. By the same authorities it is made apparent that the portal vein is posterior to the duct in the majority of bodies, but often runs entirely to the left of the duct in a posterior plane. Thompson estimates the incidence of anterior vascular relationships at approximately 30 per cent. Posterior vascular relationships occurred in 40 of Thompson's 50 dissections (80 per cent), while Daseler and his associates found them present in only 67.4 per cent. The neck of the gallbladder may overlie the upper end of the common hepatic duct, but more commonly comes into contact with the right hepatic duct and artery. Several instances of adherence of the medial aspect of an inflamed gallbladder to the common hepatic duct have been reported by Stetten (1923).

Vessels crossing the anterior surface of the hepatic duct include the cystic artery (reports of incidence varying from 15 to 24 per cent), the right hepatic artery (11 to 19 per cent), and occasionally the common hepatic artery (0 to 4 per cent).

Anterior vascular relationships were present in a total of 15 specimens in the present group (43 per cent). Both the right hepatic artery and the cystic artery were anterior to the common hepatic in a single specimen, in which the cystic artery arose from a tortuous right hepatic artery directly anterior to the duct. The cystic artery crossed the duct anteriorly in 10 other specimens (28.5 per cent), the right hepatic artery did so in 4 instances (11.4 per cent; Fig. 3b).

Posterior vascular relationships are quite common, the right hepatic crossing behind the duct in 65 per cent of the series described by Daseler and coauthors and 78 per cent of the 509 collected by Thompson. The cystic artery, or, more commonly the accessory cystic vessels, course posterior to this duct in a small number of specimens, but reports vary to such a degree (Browne, 0.7 per cent; McWhorter, 16 per cent) that no accurate estimate can be made. Browne found only 2 instances in 280 specimens, while Daseler and his associates found 12 in 500 bodies (2.4 per cent).

The cystic artery crossed posterior to the common hepatic duct in only 1 specimen (2.9 per cent) where it arose directly posterior to the duct, as is considered the normal arrangement (Fig. 3a). Direct posterior vascular relationships were, therefore, present in 74.3 per cent of the cases (including the tortuous right hepatic artery mentioned).

There were 4 specimens in the present authors' series in which an accessory right hepatic artery crossed behind the portal vein and common bile duct to reach the posterolateral aspect of the common hepatic duct, and 3 in which a replacing right hepatic artery presented a similar relationship (Fig. 4b). Thus

[1]The variability in reports of previous investigators was undoubtedly due in part to the mobility of the ducts after dissection Rotation of the dissected common hepatic and common bile ducts is easily accomplished by traction on the gallbladder or cystic duct, thereby changing a spiral (anterior or posterior) into an acute angular junction.

20 per cent of the bodies studied possessed a large artery of so-called anomalous origin which came into close approximation with the common hepatic duct.

Discussion of the vessels about the common hepatic duct must include consideration of the patterns of origin of the cystic artery from the right hepatic artery. In 14 of the 24 specimens the cystic arose on the posterolateral aspect of the common hepatic duct. In the other 9 specimens, the cystic artery arose proximal to this site and crossed the duct anteriorly (25.7 per cent). The right hepatic artery crossed anterior to the duct in 4 specimens (11.4 per cent), the cystic artery arising to the right of the duct in 3 of these specimens. In the fourth, both the right hepatic and the cystic artery crossed the duct anteriorly.

In a single specimen a tortuous right hepatic artery crossed to the anterior surface of the common hepatic duct, gave rise to the cystic artery at this point, then returned to the duct and finally ran posterior thereto in reaching the right lobe of the liver. In another instance, the right hepatic crossed posterior to the point of union of a pair of large hepatic ducts, gave rise to the cystic artery at this point, the latter vessel coursing between the ducts to reach the gallbladder (Fig. 4a). The remaining specimens were of the type in which the main cystic artery arose from an aberrant right hepatic artery close to the posterolateral aspect of the common hepatic duct (14.3 per cent).[1]

*Right and left hepatic ducts.* These ducts, as previously noted, joined extrahepatically in 33 of the 35 specimens. In the remaining 2 specimens, the livers were enlarged; hence there was found no true intrahepatic junction of the hepatic ducts. The latter situation has been considered to occur in approximately 9 per cent of specimens (Thompson).

The point of junction of the main hepatic ducts was found to lie within 0.25 to 2.5 centimeters of the hepatic tissue within the hilum of the liver (81 per cent between 0.75 and 1.5 cm.). Retraction of portions of the liver surrounding and partially overhanging the hilum was sometimes necessary in order to expose the so-called extrahepatic junction of the ducts. The comparative lengths of the left and right hepatic ducts were measured from the point at which they emerged from the liver substance to their point of junction. The right hepatic duct varied from 0.25 to 2.5 centimeters in length with a mode of 1.0 centimeter (14 specimens); the average was 0.98 centimeter, and 83 per cent measured between 0.5 and 1.0 centimeter. The left hepatic duct tended to be of slightly greater length in many specimens, due to its more oblique course. The extremes in its length were 0.5 to 3.0 centimeters (the mode being 1.0 cm., and the average 1.2 cm.); in 83 per cent of cases, the left hepatic duct measured between 0.5 to 1.5 centimeters.

Very little has been written about the hepatic ducts as they emerge from the hilum. The BNA terminology contains no definite designation for these ducts, the omission probably being due to the early teaching that these ducts, as definite entities, are frequently absent, 3 or more ducts coming together to form the common hepatic duct (Thompson). The latter author believed that definite right and left ducts were present outside of the liver in approximately 90 per cent of specimens. In the remainder of the specimens there occurred either an intrahepatic juncture, or formation of the common hepatic duct by the confluence of more than 2 ducts emerging from the hilum. Thompson made no mention of the occurrence of accessory intrahilar ducts.

Ruge's early study of the bile ducts contains his observations on 12 specimens in which the common hepatic duct arose from 3 hepatic ducts (9 instances) or 5 main ducts (3 instances) which joined in the hilum, outside of the hepatic parenchyma. He compared the triple type to the situation in the majority of mammals in which there is often found a middle hepatic duct. Ruge's observations indicated that the "middle" hepatic duct in man most often drained the region of the quadrate lobe.

[1]The common hepatic duct has another occasional relationship about which little comment is made in the literature. In 2 specimens an anomalous lobe of the pancreas paralleled the biliary ducts and extended upward to the hilum of the liver (5.7 per cent). This accessory lobe was grossly identifiable as pancreatic tissue and was continuous with the head of the pancreas, which appeared otherwise normal in both instances. The hepatic artery proper was enclosed within the pancreatic lobe in one and coursed posterior to it in the other. The common bile and common hepatic ducts were lateral in both specimens.

Descomps and de Lalaubie (1910) describe and illustrate a single case in which there were 4 main hepatic ducts, 2 equal size ducts from each major lobe of the liver, and 3 instances of 3 hepatic ducts. Kunze records 1 specimen with 3 hepatic ducts, and 1 with 4 ducts.

In classifying these reports in the more recent literature, there has been a tendency to group such specimens with those in which there are 2 main hepatic ducts and additionally small accessory ducts. The present authors have not been able to find any discussion on the frequency of occurrence of "middle" hepatic ducts extrahepatically, or in the intrahilar area where they were found.

The common hepatic duct was formed by the extrahepatic junction of definite right and left hepatic ducts in 32 specimens. Large hepatic ducts, 3 in number (2 from the right lobe), were present in 1 specimen; the left and middle ducts joined initially, the cystic duct then joined this trunk, and the large duct from the right lobe joined the common bile duct (Fig. 4a).[1] This was the only specimen in which the common hepatic was absent (2.9 per cent). There were no instances in which the cystic duct joined the right hepatic duct or the point of junction of the hepatic ducts, although such types have been reported by other writers as an occasional occurrence.

As the ducts emerge from the hilum, they are separated from the adjacent arteries and veins by areolar tissue which encloses all of the structures within the hepatoduodenal ligament and fills the intervals between them. The ducts themselves are immediately enclosed in a dense fibrous sheath. The condensation of connective tissue about the duct system of the liver begins with the smaller bile canaliculi; it then accompanies the ducts as they emerge from the parenchyma into the hilum, covering the right and left hepatic ducts, and bridging the angle formed by the converging right and left hepatic ducts. The junction of the ducts is thus partially hidden from view by the sheath which extends downward onto the common hepatic duct, to be lost in the outermost layer of this structure. The distinction between the strong and adherent sheath of the hepatic ducts and the diffuse areolar tissue which encloses all of the structures in the hepatoduodenal ligament is an important, yet neglected, feature.

The relationships of the structures close to the hilum of the liver are conventionally described as follows: the common hepatic duct lies to the right and is anterior to branches of the right hepatic artery in many instances; posteriorly, just anterior to the papillary process of the caudate lobe, the portal vein approaches the hilum and splits into a left and right branch which are covered by the ramifications of the hepatic arteries and ducts. The left branch of the portal vein enters the liver in the umbilical fissure at a point between the caudate and quadrate lobes.

According to Cole and coauthors the right branch enters the liver fully 2 inches to the right of the left branch and ½ to 1 inch posterior. They place the hepatic arteries at points slightly anterior to the respective branches of the vein, and hepatic duct midway between the branches of the portal vein but slightly anterior to a line drawn between them.

The hepatic ducts thus lie anterior to the vessels at the hilum of the liver. Anterior vascular relationships are, fortunately, quite rare. Lurje described the infundibulum of the gallbladder as overlying the structures at the upper end of the hepatoduodenal ligament in 58 per cent of his specimens, usually over the right branch of the portal vein and the ramifications of the right hepatic artery. In only a single specimen in the present series did an artery cross anterior to a right hepatic duct, the cystic duct having arisen between the left and "middle" hepatic ducts. The right hepatic artery crossed posterior to the junction of the latter two hepatic ducts. In 5 other specimens, the right hepatic artery crossed posterior to the upper end of the common hepatic duct very near its formation, the artery lying posterior to the junction of the left and right hepatic ducts in part, in 2 of the 5. Major arteries were, therefore, related to the junction of the hepatic ducts or the first 1.5 centimeters of the common hepatic duct in 6 specimens, anteriorly and posteriorly in 1 specimen (2.9 per cent), and posteriorly in 5 specimens (14.3 per cent).

[1]Some investigators would consider this an example of an accessory right hepatic duct.

In examining Thompson's account of the hepatic anatomy in 50 specimens, only 2 instances of anterior arterial relationships occurred. In 1 specimen the cystic artery crossed between the right and left hepatic ducts, coursing anterior to the right hepatic duct, much as in the specimen described. Rio Branco's incidence of this type was 10 per cent. In the other instance, an accessory cystic artery ran anterior to both hepatic ducts. In 30 figures of Kehr's, there were only 2 anterior arterial relationships; in 1 of these, a branch of the left hepatic artery crossed a low-joining hepatic duct; in the other, the right hepatic artery crossed the upper end of the common hepatic duct. In the total of 115 specimens (including the present authors' 35), there were only 5 instances of arteries presenting anterior relationships to the right and left hepatic ducts to their junction, or to the first 1.5 centimeters of the common hepatic duct (4.4 per cent).

The hepatic arteries otherwise presented a lateral and posteroinferior relationship to the hepatic ducts. The terminal extrahepatic branches of the right hepatic artery were lateral, while the left hepatic artery branches lay medial to the corresponding hepatic ducts as they entered the hilum of the liver. This relationship obtained in the first 2 centimeters of the intrahepatic course in 7 out of the 10 specimens in which an intrahilar dissection was carried out. In 3 specimens a small branch of the right hepatic artery coursed medialward, crossing the posteroinferior aspect of the right hepatic duct or one of its tributaries. The portal vein maintained its posterior relation to ducts into the hilum.

The right and left hepatic arteries frequently subdivided into two or more branches before entering the hilum. Descomps and de Lalaubie listed the extent of extrahepatic branching and distribution for both the right and left hepatic arteries in 100 specimens. The right hepatic entered the liver as 3 branches in 42 per cent, 2 branches in 26 per cent, 4 branches in 16 per cent, 5 branches in 6 per cent, and a single branch in only 4 per cent. This vessel coursed to the right lobe only in 62 per cent and sent an additional branch to the left lobe of the liver in 34 per cent. The left hepatic artery entered the liver as 2 branches in 36 per cent, a single branch in 22 per cent, 3 branches in 22 per cent, 4 branches in 12 per cent, and 5 branches in 8 per cent. This artery was distributed (extrahepatically) to the left lobe only in 76 per cent, sent an additional branch to the caudate lobe in 12 per cent, or to the quadrate lobe (10 per cent).

The portal vein branched into a right and left trunk in all of the present authors' specimens. There were no extrahilar divisions of these trunks. Descomps and de Lalaubie reported a bifurcation of the right branch of this vein in 12 per cent, while Cole and coauthors described the vein as entering the hilum as a single trunk in 10 per cent of specimens.

The topography of the anterior surface of the liver was studied in an attempt to determine whether definite landmarks were present which would aid the surgeon in locating a common hepatic duct remnant or stump. Many depend upon the aspiration of bile from the area near the hilum of the liver or blood from the portal vein when the landmarks within the hepatoduodenal ligament are obliterated by scar tissue.

The quadrate lobe of the liver extends from the umbilical fossa, which contains the falciform ligament, to the medial edge of the fossa of the gallbladder (Fig. 2a). This lobe varies in width and configuration as the gallbladder fossa varies in location and obliquity. Its hilar margin presents a somewhat rounded apex in the great majority of specimens. The width of the quadrate lobe was recorded in 33 specimens. The mean width was 4.0 centimeters, the extremes in width 1.0 to 8.0 centimeters, with 88 per cent between 2.0 and 6.0 centimeters.

The relationship of the converging hepatic ducts and the upper end of the common hepatic duct to the hilum of the liver is not easily altered, due to the strong sheath about the ducts and the connective tissue binding them to the adjacent vessels. Previous trauma or inflammatory processes should have little effect upon the location of the ducts or portions thereof near the hilar region.

The point at which the common hepatic duct was formed by the converging hepatic

ducts was noted in relation to the hilar "apex" of the quadrate lobe. The junction was located at the apex in 18 out of 33 specimens (54.5 per cent, Fig. 2a), and was 0.5 to 1 centimeter to the right of the apex in 11 additional specimens (33.3 per cent). Thus, in 88 per cent of the specimens the superior extremity of the common hepatic duct was at the midpoint of the hilar margin of the quadrate lobe, or within 1 centimeter, toward the gallbladder fossa. In only 4 instances (12 per cent) did the ducts emerge closer to the gallbladder fossa than to the apex of the quadrate lobe (Fig. 2b) and in 3 of these, the quadrate lobe was so narrow that they did not lie more than 1.5 centimeters from its apex. In no specimen did the common hepatic duct leave the hilar region more than 0.5 centimeter to the left of the hilar apex of the quadrate lobe.

The right hepatic duct courses laterally to become truly intrahepatic very close to the base of the fossa for the gallbladder. The left hepatic duct runs medialward to the umbilical fossa before penetrating deeply into the left lobe of the liver. The intrahilar course of these ducts may be estimated from the width of the quadrate lobe.

Of interest to the surgeon who sometimes finds it necessary to insert tubes into the right and left hepatic ducts is the occurrence of not only accessory extrahepatic ducts (discussed hereinafter), but also of ducts which join the main hepatic ducts within the first 2 centimeters of their intrahepatic course.

The hilar area of the liver was subjected to further study in 10 specimens, and it was found that there were one or two ducts joining the point of confluence of the main right and left hepatic ducts in 5 specimens (50 per cent). These tributaries emptied into the angle formed by the converging ducts in a plane parallel to that of the departing common hepatic duct and were one-half to one-third the diameter of the main ducts. Specifically, there was a single tributary emptying into the angle in 4 (Fig. 3a) and 2 tributaries in 1 specimen (Fig. 3c). These ducts were intrahilar and seemed to drain the area of the quadrate lobe. They may well represent the "middle" hepatic duct seen rarely outside of the hilum, as described by Ruge.

TABLE V.—FREQUENCY OF OCCURRENCE OF ACCESSORY HEPATIC DUCTS

| Author | No. of specimens | No. of accessory ducts | Percentage occurrence |
|---|---|---|---|
| Beaver | 57 | 5 | 9 |
| Brewer | 100 | 1 | 1 |
| Descomps and de Lalaubie. | 50 | 10 | 20 |
| Eisendrath | 100 | 0 | 0 |
| Flint | 200 | 29 | 15 |
| McWhorter | 37 | 1 | 3 |
| Piquand | 40 | 10 | 25 |
| Ruge | 43 | 11 | 26 |
| Thompson | 50 | 3 | 6 |
| Lurje | 194 | 22 | 11 |
| Michels | 200 | 36 | 18 |
| Johnston and Anson | 35 | 11 | 31 |

In addition, the right hepatic duct received a tributary of moderate size within the first centimeter of its intrahepatic course in 3 specimens (30 per cent, Fig. 3b); the left hepatic duct received none. The single specimen in which 2 additional ducts drained into the angle also possessed a tributary of the right hepatic duct and is, therefore, included in both groups (Figs. 3b and 3c). In only 3 out of the 10 specimens the right and left hepatic ducts were single channels from their juncture to 2 centimeters within the hepatic tissue. Although such a small group of specimens will not permit prediction of probable occurrence of types, it should serve to bring to attention the frequency of accessory intrahilar hepatic ducts and branches.

The anomalies of the hepatic ducts include termination of the right hepatic duct in the gallbladder at its liver bed (as in Kehr's Fig. 62c), or in the cystic duct (both extremely rare). Accessory hepatic ducts are derived more frequently from the right lobe of the liver than from the left; they drain at varying levels into the right hepatic, the cystic, or the common hepatic duct. Flint states that these accessory ducts leave the liver at the extreme right end of the portal fissure, and lying at first on a deeper plane than the cystic duct, course downward in a course anterior to the right hepatic artery. Flint divided these ducts into three groups dependent upon their level of junction: junction with the right hepatic duct or the upper half of the common hepatic duct (9 of the 29 accessory ducts observed in his 200 dissections); junction with the lower half of the common hepatic duct (9 examples); junction at the confluent point

of cystic and common hepatic ducts (10 of 29).

Accessory ducts of the first type are obviously of less interest to the surgeon carrying out a cholecystectomy than those in the other two categories, but the presence and location of emergence of these accessory ducts are important to the surgeon in seeking the stump of the hepatic duct in the hilar area. Their size varies from that of the normal hepatic ducts to the caliber of a minute twig. Kunze's Figure 4 shows an accessory duct leaving the right lobe of the liver lateral to the fossa for the gallbladder.[1]

Thompson collected 51 examples of accessory ducts and found that 47 (92 per cent) arose from the right lobe. Table V shows the overall incidence of accessory hepatic ducts and demonstrates the extreme variation between individual reports.[2]

The present writers found 11 examples of accessory hepatic ducts, not including the intrahilar tributaries already described. Such incidence is very high (31.4 per cent); it represents the results of very careful dissection of the proximal end of the biliary ducts, including the tracing of these small structures into the hilar and intrahepatic areas.

Of the 11 accessory ducts, 5 were of a type hitherto undescribed, although Thompson's Figures 10 and 20 show an accessory duct which might have proved to be of this type had they been traced further into the hilum. In these instances, the small duct arose from the right hepatic duct, coursed lateral to a major artery, and rejoined the common hepatic duct or the right hepatic duct. The accessory channel was separated from the junction of the hepatic ducts by the right hepatic artery in 3 (Fig. 3b), an accessory right hepatic artery in 1, and the cystic artery in the remaining instance (Fig. 4b). The latter artery arose from the right hepatic very close to this channel in all of these. Were this type of duct classified as an accessory biliary channel rather than as a true accessory duct from the liver substance, current incidence would be more in keeping with previous reports (17 per cent). In 1 of the 5 specimens there occurred both this type of accessory duct and a duct from the right lobe of the liver to the common hepatic (Fig. 3b).

The accessory right hepatic duct ran from the right lobe or the liver to the cystic duct in 4 instances (Fig. 4c). In 1 specimen a single accessory duct joined the common hepatic duct (Fig. 4d). The final example of an accessory right hepatic duct has already been described as the instance in which the common hepatic duct was absent; a very large accessory duct joined the common bile duct (Fig. 4a). The accessory ducts came into close contact with the posterior surface of the cystic duct in the last 2 specimens.

No instance of accessory left hepatic duct occurred in the 35 specimens. There were 2 small duct-like structures from the right lobe which could not be definitely classified as either veins or ducts, and in 9 specimens small veins were present in the distribution area of accessory right hepatic ducts. These were classified as such on the basis of their superficial distribution on the cystic duct or gallbladder, or drainage into a branch of the portal vein intrahepatically. It would seem that the regularly described scheme of venous drainage of the gallbladder, by veins which join the hilar or extrahepatic course of the right portal vein, does not occur in most specimens. More commonly, the veins of the gallbladder drain into a small ascending trunk, which, arising in the pancreatic area and paralleling the portal vein on its lateral aspect, enter the hilum and hepatic tissue separately, or by

[1]Less frequently observed variations include small accessory ducts from the left lobe of the liver joining the left hepatic duct (Beaver 1929), double accessory right ducts draining into the right hepatic or common hepatic duct, and double accessories, one right and one left accessory duct (latter 2 examples reported by Descomps and de Lalaubie).

[2]The variance in reports may depend upon the method employed and upon thoroughness of the dissection. Mentzer found 8 examples of cyst-hepatic ducts (those hepatic ducts draining into the side of the gallbladder or into the cystic duct) in 96 dissections (8.3 per cent), a much higher incidence for this particular accessory duct than reported elsewhere. He stated that many small ducts were grossly indistinguishable from small veins draining the gallbladder and felt that microscopic examination of sections of these small structures was necessary to arrive at a true value of their incidence. Mentzer is one of the few authors who has called attention to the difficulty of identifying, by gross means, the small, duct-like structures from the gallbladder or cystic duct to the gallbladder fossa or hilum of the liver. There will be little agreement among results of various authors until the specimens of gross dissection are subjected to microscopic examination.

In 3 of the present authors' specimens, this technique was used merely to corroborate the gross identification. One of the vein-like structures which ran from the cystic duct deep into the hilum and right lobe of the liver was a very small artery (diameter 1 mm.) with two accompanying veins.

short veins which reach the fossa of the gallbladder or the lateral angle of the hilum of the liver.

The cystic duct, gallbladder, and hepatic arteries were studied in the 35 specimens, the results of which will be presented briefly for the purpose of inclusion in any future compilation studies of the area.

*Cystic duct.* The cystic duct is a tube of variable length, size, and course. Because of its considerable clinical importance, structure, and relationships of the duct have been accorded repeated emphasis in the literature. The pitfalls presented to the surgeon by the close proximity of such structures as the hepatic artery or accessory ducts have been discussed frequently.

The length of the cystic duct in 35 specimens varied from 1.5 to 4.0 centimeters (before separation, in cases of parallelism), giving a mean value of 2.7 centimeters. The same factor of increased length, after careful separation of the cystic from the common hepatic duct, applies to the former duct (shown for the latter in Table II). The longest cystic duct was 6.0 centimeters (after separation). Lander and coauthors found that the majority fell within 1.0 to 3.0 centimeters, and listed the extremes as 0.5 to 4.5 centimeters. Brewer reported a range of 0.5 to 2.5 inches (1.3 cm. to 6.5 cm.) with an average of 1.2 inches (3.0 cm.). McWhorter found an average length of 2.5 centimeters in 35 specimens. In general, the recorded figures center about a mean length of 2.0 to 3.0 centimeters before separation of the long or short parallel types of junction.

The vascular relationships to the cystic duct have been presented by many authors. The combined figures of Brewer and Thompson (totalling 100 specimens) indicated anterior arterial relationships in 20 to 28 per cent and posterior arterial relationships in 18 per cent. A pair of arteries, anterior and posterior to the duct, occurred in 3 of Brewer's 50 specimens.

In 18 specimens (51.4 per cent) of the authors' series the duct possessed no arterial relationships. In 9 specimens (25.7 per cent) the cystic artery lay in close anterior approximation to the duct, lying anterior and superior (cephalad) to the duct in a somewhat parallel course. In 2 of the 9 specimens the duct had posterior arterial relationships, anterior and posterior arterial relationships thus existing in 5.7 per cent. The posterior vessels were an accessory right hepatic and a very tortuous right hepatic in a single instance each.

Posteriorly the accessory right hepatic coursed close to the cystic duct in all 4 specimens in which it occurred, and 2 of the 3 replacing right hepatic arteries did the same, the other replacing vessel coursing further medially. The right hepatic branch of the common hepatic artery coursed posterior to the cystic duct in a single specimen, and the cystic artery paralleled the duct posteriorly in another. In 2 specimens, 1 of which has already been described as having both anterior and posterior arteries, the right hepatic artery presented a tortuous course with the formation of a small loop in and about the angle between the cystic and common hepatic ducts. The relationship of the cystic duct to accessory hepatic ducts has been discussed in a previous paragraph.

The cystic artery has already been discussed in respect to its relationship to the common hepatic duct and in regard to its mode of origin. In the present authors' series, 25 instances (71.4 per cent) were encountered in which a single cystic artery arose from the right hepatic. In only 6 specimens (17.1 per cent) 2 cystic arteries were present; both arose from the right hepatic artery in 4 of these, both from the accessory right hepatic artery in 1; in another specimen an accessory cystic artery arose from the appendiceal artery (the vermiform process being bound to the gallbladder by adhesions), the other cystic artery arising in the regular way from the right hepatic. In 4 cases (11.4 per cent of the total group) the single cystic artery was of the replacing type; of these, 3 arose from replacing right hepatics and 1 from an accessory right hepatic. The cystic artery arose typically as a single branch of the right hepatic in the angle between the cystic and common hepatic ducts (Calot's triangle) in only 14 of the 24 specimens (40 per cent) in which the latter vessel had crossed posterior to the common hepatic duct in the manner regarded as typical.

*Gallbladder.* The vesica fellea exhibits very few major anomalies in man. Variations in its position on the inferior surface of the liver, degree of intrahepatic location, extent of peritoneal investment, congenital absence, and reduplication (partial or complete) have been reported. Boyden has reviewed this subject thoroughly and related the anomalies in man to the various types of gallbladder found normally in many of the domestic animals. Schachner collected 11 reports of gallbladders located to the left of the round ligament of the liver. Intrahepatic or buried gallbladders have been reported in a number of specimens.

Neither of the latter variations occurred in the present series, although it was observed that the depth of the fossa for the gallbladder varied from 0.25 to 2.0 centimeters. The usual extent of peritoneal investment (two-thirds to three-fourths of the anterior surface of the gallbladder) would represent in 20 of the 30 specimens (67 per cent) in which this feature was recorded. More than three-fourths of the surface was in contact with peritoneum in 3 specimens (10 per cent), 1 of these having a mesentery-like attachment to the liver in the anterior portion. In 7 cases the gallbladder had less than two-thirds of the area covered; in 2 instances of these, as little as one-tenth of the surface was covered by peritoneum.

The relationship of the anterior tip of the gallbladder to the anterior margin of the right lobe of the liver has been recorded by several authors, Lurje (1937) classifying them as supramarginal (not extending downward to the free edge of the liver), marginal, and inframarginal (pendent below the free edge of the liver, and hence more easily palpable). The present authors classified 17 of 29 of their specimens as inframarginal (58.5 per cent), 8 as marginal (27.6 per cent), and only 4 as supramarginal (13.8 per cent). Lurje's figures were 53.1 per cent, 13.9 per cent and 33 per cent, respectively, for these types.

Attachments of the gallbladder to the adjacent transverse mesocolon occurred in 12 specimens, to the duodenum in 2, and to the appendix and highlying cecum in 1 specimen. Neither medial displacement of the gallbladder nor duplication of vesica fellea was seen.

HEPATIC AND RELATED ARTERIES

*Hepatic artery proper.* This vessel arose from the celiac artery in all specimens of the current series. The vessel was absent as such in the 3 specimens in which a replacing right hepatic artery arose from the celiac or the superior mesenteric artery (2 specimens and 1 case, respectively); a hepatic proper and common hepatic were present, but in each case, continued as the left hepatic artery only.

*Gastroduodenal artery.* This artery of supply to the stomach and duodenum arose from the hepatic proper in all of the specimens studied.

*Common hepatic artery.* The common hepatic is the continuation of the hepatic proper after the latter has given rise to the gastroduodenal artery. The common hepatic was present as such in 32 specimens (91.4 per cent), giving rise to both left and right hepatic branches. It gave origin to left hepatic branches only in 2, and in a single unusual specimen gave rise to a vessel which entered the medial border of quadrate lobe only, the two main lobes then receiving their arterial supply from a replacing right hepatic and an accessory left hepatic. The common hepatic was very short (0.25 to 1.5 cm.) in 7 specimens.

*Right gastric artery.* The gastric artery on the right arose from the common hepatic artery and thus distal to the origin of the gastroduodenal, in 18 out of 31 vessels recorded (58.1 per cent). The artery originated in a common trunk with the left hepatic artery in 9 specimens, from the continuation of a hepatic proper vessel going entirely to the left lobe of the liver in 2 (6.5 per cent) and from the hepatic proper and gastroduodenal arteries in a single instance each (3.2 per cent). There was only 1 example of an accessory right gastric, this branch arising from the accessory left hepatic artery.

*Left hepatic artery.* The left hepatic was present as a branch of the typical common hepatic in 32 specimens (91.4 per cent), the so-called common hepatic giving rise in the remaining 3 to the left hepatic artery branches solely. An accessory left hepatic artery was present in 9 specimens (22.9 per cent), arising as a single vessel from the left gastric artery in every instance.

*Right hepatic artery.* The right hepatic took origin from the common hepatic in 32 of the 35 specimens (91.4 per cent). An accessory right hepatic artery was present in 4 of these specimens, arising from the superior mesenteric artery in each instance. In 3 specimens the right lobe of the liver received its entire arterial supply from a replacing right hepatic vessel. In 2 cases the replacing vessels arose from the celiac axis, in 1 from the superior mesenteric artery. Aberrant right hepatic arteries were, therefore, present in 20 per cent of the authors' specimens, taking origin from the superior mesenteric artery in 14.3 per cent, the celiac axis in 5.7 per cent.

## SUMMARY

The supraduodenal portion of the common bile duct was absent as such, due to a low insertion of the cystic duct in 20 per cent. Supraduodenal arterial relationships were present anteriorly in 20 per cent; the posterior superior pancreaticoduodenal artery crossed the retroduodenal portion of the duct in 80 per cent of the authors' specimens. In 6 of 7 cases of aberrant right hepatic arteries, the vessel crossed close to the posterolateral aspect of the common duct.

The common hepatic duct was joined by the cystic duct at an acute angle in 63 per cent of cases. A short parallel type junction was present in 20 per cent, a spiral type in 17 per cent. The hepatic duct was absent as such in only a single specimen (2.9 per cent). In relation to the duct, arteries were present anteriorly in 43 per cent, posteriorly in 74.3 per cent, and aberrant right hepatics posterolateral to the duct in 20 per cent.

The junction of the right and left hepatic ducts occurred extrahepatically in 94.3 per cent of specimens, the junction taking place from 0.75 to 1.5 centimeters away from the hepatic tissue within the hilum in the majority of specimens. The left hepatic duct tended to be slightly longer than the right.

Regarding the relationship of the structures at the hilum of the liver, it may be said in summary that arterial branches were anterior to the hepatic ducts or the first 1.5 centimeters of the common hepatic duct in only 1 specimen (2.9 per cent); the arteries were almost always situated to the outer side of the corresponding duct (medial to the left and lateral to the right hepatic duct), the portal vein subdivisions posterior.

The quadrate lobe was found to range from 2.0 to 6.0 centimeters in width in majority of specimens (mean width, 4.0 cm.). The emergence of converging right and left hepatic ducts of the common hepatic duct was found to occur opposite the midpoint of the hilar margin (often apical in contour) of this lobe in 54.5 per cent and within 1.0 centimeter to the right in an additional 33.3 per cent. In 3 of the 4 specimens in which the ducts emerged nearer the gallbladder fossa than the first-named site, the apex of the quadrate lobe was very narrow and the ducts did not lie more than 1.5 centimeters from its apex.

Accessory intrahilar hepatic ducts drained into the angle of the confluent right and left hepatic ducts in 50 per cent of 10 intrahilar dissections. A tributary of moderate size joined the right hepatic duct within the first centimeter of its intrahepatic course in 3 specimens (30 per cent). Only 3 of the 10 specimens exhibited right and left hepatic ducts which did not receive accessory "middle" hepatic ducts, or significant tributaries in the first 2.0 centimeters of their intrahepatic course.

Extrahepatic accessory ducts were present in 31 per cent, all from the right lobe of the liver or the right hepatic duct.

The hepatic arteries, the cystic duct and gallbladder have been discussed briefly.

Anatomically the quadrate lobe would appear to be of aid in locating the emergence of the hepatic ducts from the hilum of the liver when the structures within the hepatoduodenal ligament are obscured by scar tissue. The relative infrequency of major arteries lying anterior to the hepatic ducts near the hilum of the liver would suggest an approach which would follow the quadrate lobe closely, dorsalward to the hilar area.

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# A CLOSED GRAVITY TECHNIQUE FOR THE PRESERVATION OF WHOLE BLOOD IN ACD SOLUTION UTILIZING PLASTIC EQUIPMENT

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THE most significant contribution to the collection and storage of blood continues to be the use of ACD[1] as the anticoagulant and nutrient. Improvements in technique to protect the donor, ensure maintenance of sterility, increase the stability of the blood, and make infusion more effective are desired. War and disaster introduce logistic problems to stimulate the search for more ideal blood handling equipment. New plastic equipment and a technique for the collection, storage, and infusion of blood exploiting the advantages of ACD are presented. Hematologic evidence supporting the advantages of this technique is presented elsewhere (1).

The equipment, Figure 1, consists of a laminar flow phlebotomy needle, an integral donor tube and a collapsible bag of polyvinyl resin so designed that the unit is sterilized, assembled and filled, ready for use, by exposure to saturated steam at 121 degrees C. for 30 minutes.

Phlebotomy is accomplished with a specially ground and polished stainless steel (type 304) needle. The cannula extends through the entire hub. It is flared to meet the wall of the donor tube to preserve laminar flow and thus prevent platelet aggregation. This design also facilitates cleaning the needle for re-use. The molded nylon (type FM 3001) hub has opposed male ends tapered to fit and seize the plastic tubing and protective sheath.

An adherent, hemorepellent film of tris (2 hydroxyethyl) dodecyl amine is applied to the steel part of the needle to delay the initiation of clot formation. Blood will flow continuously for over 2 hours at the rate of 17 cubic centimeters per minute through a coated laminar flow needle lying in an antecubital vein impelled by venous pressure alone (3).

The polyvinyl resin is chemically inert to biologic fluids and is nonirritating to tissue. Its glossy surface is hemorepellent. Tubing made of it is elastic and flexible enough so that a needle lying in a vein will determine the position of the tubing even though there is limited motion of the vein. The plastic is clear, colorless, and transparent so that the provision of viewing chambers is unnecessary. A 0.4 millimeter film of this plastic is not an osmotic membrane; it is a bacterial barrier and transmits water vapor at the rate of 0.025 milligram per square centimeter per 24 hours at 20 degrees C.

The tubing for the donor and recipient sets is extruded with a lumen 3 millimeters in diameter and a wall 0.5 millimeter thick. It can be sealed by internally generated heat applied as radio frequency energy or by setting an overhand knot tightly.

The collection, storage, and administration of the blood is accomplished in a collapsible bladder made of 12.5 centimeter lay flat tubing 0.25 millimeter thick by fusing the ends and tubing entries. The blood is introduced into the bag through the 60 centimeter donor tube which is filled with anticoagulant solution and occluded at its entry to the bag with a coated stainless steel sphere to prevent aspiration of air prior to phlebotomy.

The blood or those fractions separable by gravity are removed from the bag through suitable delivery tubes. Externally these are similar and consist of two lengths of 6 millimeter tubing 2.3 millimeters long sealed in the end of the bag. A diaphragm 0.5 millimeter thick forms a barrier across the tubes 5 millimeters from the open end. The outer ends of the tubes are enclosed in a closed pouch to prevent bacterial contamination. The redun-

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[1]Trisodium citrate, 2.22 per cent; citric acid, 0.8 per cent; dextrose, 2.45 per cent.

dant plastic skirts on either side of the pockets bear data regarding the expiration date, group, and type of blood arranged so that appropriate characters can be punched out to leave indelible identification. The inner ends of the delivery tubes differ in that the one for plasma removal terminates in a simple throat; that for the removal of whole blood or cells extends 4 centimeters into the bag and is perforated by 20 holes 2 millimeters in diameter to catch the gelatinous mass of red cells that occasionally forms during prolonged storage and prevents stoppage of tube connecting with filter.

The assembled bag and donor set are rinsed with distilled water, 75 cubic centimeters of ACD Solution A (U.S.P. XIV) is added, the air is expressed from the system, and the steel ball is positioned. The needle with its protective sheath in place is coupled to the donor tube and the finished assembly is sterilized by exposure to saturated steam at 121 degrees C. for 30 minutes.

Proof of the hematologic advantages of the design of the plastic equipment is the fact that blood can be drawn from a donor into an empty bag and hermetically sealed without activating the clotting mechanism. Whole blood, without anticoagulant, remains liquid for 6 to 8 hours at 25 degrees C. under these conditions.

Logistic advantages of this equipment are many. The bag of ACD with its integral donor set weighs 115 grams packaged in an aluminum tube—16 per cent of the weight of a conventional blood container. The integral donor set obviates a separate part to be procured, inventoried, and distributed. The equipment can be shipped or stored in temperatures ranging from minus 56 to plus 76 degrees C. As packed commercially, 4 bags sealed in a tin can weigh 586 grams and occupy 1,100 cubic centimeters—13 per cent of the space occupied by conventional equipment with comparable function. The bags weigh 620 grams when full of blood in contrast to 1,070 grams for a full bottle. Two bags of blood can be shipped in the space occupied by 1 bottle. The cost of transporting plastic equipment charged with ACD to the donor center and returning the blood to the point of origin is 25 per cent of that for glass.

The recipient set (Fig. 2) consists of a combination filter and drip chamber fashioned of a 14 centimeter length of plastic tubing, 20 millimeters in diameter with a stiff 0.5 millimeter wall, sealed at either end to appropriate lengths of 3 millimeter plastic tubing. The filter in the chamber is made of 70 mesh woven nylon tubing, intussuscepted on itself to provide 64 square centimeters of filter area, with the open ends dielectrically sealed about the entry tube. The drip chamber is formed by constricting and sealing the bottom of the filter chamber about a nipple of 2 millimeter tubing. The filter and drip chambers do not collapse under a negative pressure of 110 centimeters of water and withstand 300 millimeters of mercury pressure during infusion. The piercing coupler is connected to the short entry tube; the 17 gage venipuncture needle is fixed at the end of the longer venipuncture tube. Pyrogen free water is rinsed through the assembled recipient set and the needles are covered with a protective sheath prior to sterilization as described.

The technique for using the bags is simple. The donors lie supine with a pneumatic tourniquet[1] applied to the arm. The skin overlying the antecubital fossa is disinfected by scrubbing with soap and water until a stiff lather is produced. This is removed by applying tincture of iodine U.S.P. XIV. The iodine is permitted to dry and the excess is removed with 40 per cent isopropyl alcohol. A wheal of 1 per cent procaine hydrochloride is raised in the skin and the tissues about the vein are infiltrated. The tourniquet is distended to 60 millimeters of mercury pressure. A loose overhand knot is formed in the midportion of the donor tube and the bag is suspended on a spring scale with the delivery tubes uppermost. The protective sheath is removed from the phlebotomy needle by pushing it onto the hub slightly to loosen its grip on the nylon and then twisting it off. Phlebotomy is accomplished (Fig. 3). The stainless steel sphere is milked upward out of the donor tube to permit the blood to flow by gravity. When 640 grams have been collected, the knot is set tightly to seal the bag (Fig. 4). The donor

[1]An aneroid sphygmomanometer with child size hook cuff is best.

Fig. 1.

Fig. 1. Plastic bladder for the collection, storage, and infusion of blood. The bladder and integral donor tube are filled with 75 cubic centimeters of anticoagulant-nutrient solution. A few bubbles of air have been admitted to make the solution obvious. The delivery tubes for removal of plasma or coupling with a recipient set with their protecting pouches are at the lower left. Insert, Longitudinal section of the male hubbed needle shows laminar flow channel at connection with plastic tubing.

Fig. 2.

Fig. 2. One piece plastic recipient set consisting of combination filter and drip chamber. Piercing coupler is at upper left.

tube is severed on the donor side of the knot so that appropriate pilot tubes can be filled. The pressure is then released from the tourniquet and the needle is withdrawn from the vein. It can be coupled with the end of the donor tube to protect its sharpness.

The blood in the donor tube is sealed off in aliquots by applying radio frequency energy across the tubing while it is compressed in the jaws of a sealer (Fig. 5). The final seal is made at the junction of the donor tube with the bag.

Samples of citrated blood can be preserved for cross matching by stripping the blood from the donor tube and permitting it to refill with citrated blood prior to sealing off the tube at the bag. This is done by flexing the tube over the edge of a throat stick just proximal to the knot and drawing the stick to the bag, leaving collapsed tubing distal. Serum for serology and grouping can be obtained by sealing off whole blood in the end of the tube prior to stripping the blood from the remainder. Segments of the donor tube are cut free and centrifuged in a 15 cubic centimeter trunnion cup filled with water. An aluminum tubing clip is applied at the plasma-red cell interface and the seals are cut from either end. Individual drops of the plasma or the red cells can be ejected by a slight pressure on the appropriate tube.

The hermetically sealed bag is suspended from a metal stand. The pilot tubes may be inserted in the identification tag fastened to the bag. The unit is refrigerated at 4 degrees C. plus or minus 1 degree.

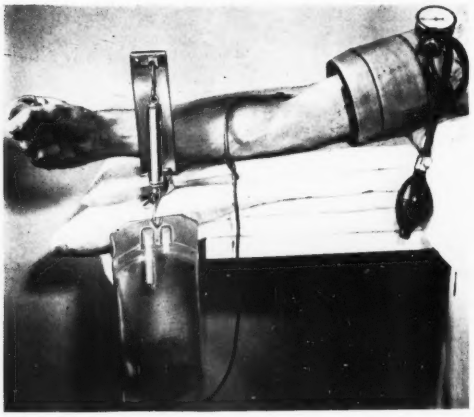

Fig. 3. Collection of blood by gravity through integral donor set into plastic equipment. The quantity of blood removed is indicated on the spring scale.

Fig. 5. Jaws of the radio frequency sealer applied across the donor tube fuses the tubing to effect a hermetic seal. Insert, Segments of donor tube can be sealed off to serve as pilot tubes.

The blood is administered by cutting off the end of the protective pouch about the blood delivery tube (Fig. 6). The sheath is removed from the coupler and the cannula is twisted into the lumen of the delivery tube simultaneously to penetrate the diaphragm and couple with the delivery tube. The bag is suspended from a gravity pole (Fig. 7) by means of a spring scale so that an accurate indication of the volume infused is available. The filter chamber is filled half full of blood by holding it inverted with the drip chamber uppermost after the protective sheath is removed from the 17 gage infusion needle. When the filter is properly filled, it is righted and the air is expelled from the recipient tube prior to venipuncture. The rate of infusion can be regulated by varying the height at which the bag is suspended above the recipient's vein or by applying a clip across the recipient tube just proximal to the infusion needle.

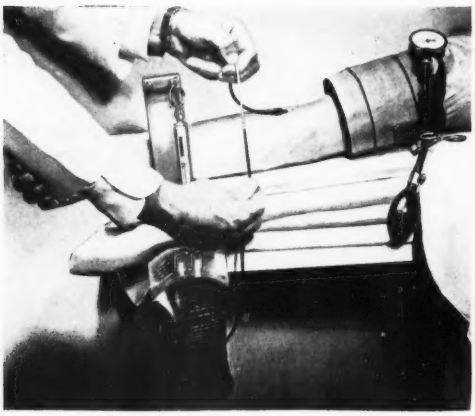

Fig. 4. Pulling the knot tight in order to seal the donor tube.

Fig. 6. Cutting off the protective pouch to gain access to the outer end of the sterile delivery tube.

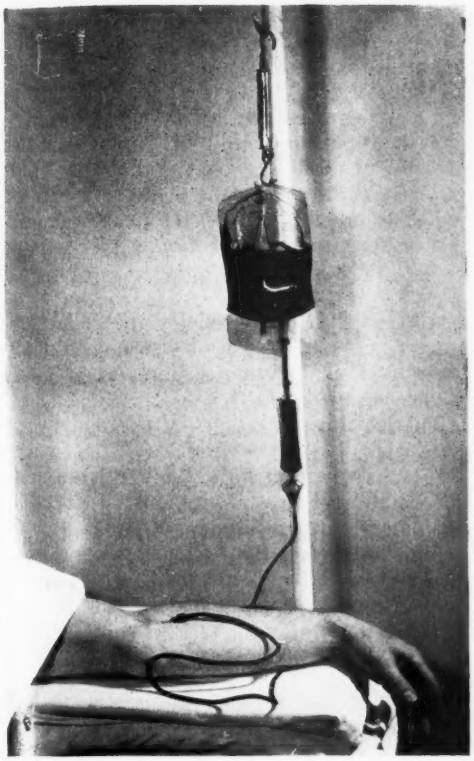

Fig. 7. Blood is infused by inserting the piercing coupler into the delivery tube and suspending the bag for gravity flow.

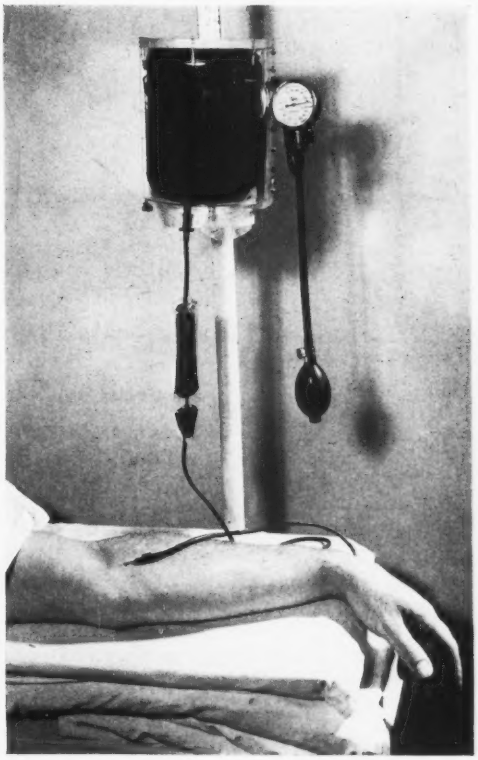

Fig. 8. The full bag of blood with the recipient set attached is compressed in a plastic press to permit positive pressure infusion without danger of air embolism.

Positive pressure infusion is readily performed by slipping the bag, with a recipient set attached, into a pneumatic press where controlled pressure is applied to force the blood out of the bag (Fig. 8). The contents of the bag (575 c.c. of ACD blood) can be forced intra-arterially through a 14 gage cannula against a systolic pressure of 100 millimeters in 1 minute by applying 300 millimeters of mercury pressure to the press. The rate of flow through a 15 gage needle is indicated in Figure 9(2). The press consists of a hemicylindrical chamber (radius 7 cm., height 16 cm.) fashioned of $\frac{5}{16}$ inch plexiglass. The bottom is solid; the top slides off to permit a full bag to be slipped in. A conventional sphygmomanometer cuff is supported against the flat side of the chamber by hanging the long end of the cuff over a transverse rod mounted near the top of the flat side. The tubes are brought out of the chamber through a pair of holes positioned to retain the cuff against the flat wall. Pressure is built and measured in the usual manner. The full bag of blood with the recipient set attached is slipped into the space in front of the rubber cuff and the top is closed. A bail may be inserted into appropriate holes to suspend the press either in the inverted position for infusion or upright for withdrawal of plasma. Appropriate pressure is applied to attain the desired flow.

Plasma can be removed from the bags following either sedimentation or centrifugation. For the latter, the bag is placed in the conventional 600 cubic centimeter trunnion cup and

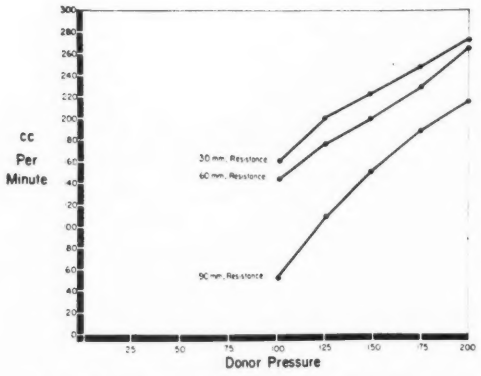


Fig. 9. Rate of blood flow through a 15 gage needle. Recipient pressure was kept constant, the donor pressure being varied. Courtesy of S. F. Seeley, *Current Reseaches in Anesthesia and Analgesia* (2).

the space about the bag is filled with water. After properly balancing the opposed cups, the cells are packed by 20 minutes' exposure to 750× gravity centrifugal force. The bag is removed from the centrifuge and placed in the pneumatic press described. The plasma delivery tube is exposed by cutting away the protective pouch and the diaphragm is pierced by a coupler connected by tubing to the plasma collecting container. Air is pumped into the press to force the plasma out of the bag. As the plasma-red cell interface rises into the delivery tube, a clamp is applied to effect accurate separation. By this technique, 99 per cent of the plasma can be removed. The residual cells are packed to a hematocrit of over 98.5 per cent by centrifugation; 85 per cent by sedimentation. The cells can be resuspended or washed by using the plasma delivery tube as the port for adding the appropriate solution. When resuspension is completed, the delivery tube is resealed by clamping it in the jaws of the radio frequency sealer and applying current for 5 seconds. The resuspended red cells are infused by the technique described for the administration of blood.

## SUMMARY

Apparatus is presented for the collection, storage, and administration of whole blood by using a closed gravity technique and ACD Solution A.

The logistic advantages of the equipment are outlined.

A technique is given for sealing off aliquots of blood for subsequent cross matching in the permanently attached donor tube.

A method for positive pressure infusion, both intravenous and intra-arterial, is presented.

A technique for centrifugation and separation of plasma is described.

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# BEDSIDE UROLOGICAL X-RAY EXAMINATION OF THE SEVERELY INJURED PATIENT

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A SEVERELY injured patient who has possible multiple injuries requires the close co-operation and keen judgment of a team of physicians in the various surgical specialties. The problem for the urological consultant is not so much that of detecting the presence of a genitourinary trauma as it is of knowing the exact extent of the injury. Recent reports in the literature have shown that since there is no correlation between the intensity of the traumatism, the clinical signs, the symptomatology, and the gravity of the urinary tract lesion, the patient should be investigated urologically by roentgenography as quickly and completely as possible. It is only by this approach that a genuine anatomicopathologic diagnosis can be made (1, 5, 8, 11). However, severely injured patients whose general condition contraindicates movement to the x-ray department for roentgenological examination present an especially serious problem in urological diagnosis and management. The difficulty is increased if, in addition to the genitourinary trauma, there is associated visceral and/or bony lesions. In these instances the latter may be of such magnitude as to be considered of paramount importance and the kidney or the bladder trauma as trivial in nature. The necessity of obtaining diagnostic roentgenograms at the bedside in this group of patients is readily apparent. A careful review of the world literature has failed to reveal a description of a standardized technique by which this could easily be done. It is a prerequisite in the evaluation of conservative versus operative intervention if we are to institute rational therapy in time for it to be of real value.

Roentgenographic visualization of the urinary tract by the use of opaque contrast substances requires the use of the Potter-Bucky diaphragm(2). This permits only radiation travelling in the direction of the x-ray beam to strike the photographic film, thus producing pictures with sharper contrast. Films taken without the Bucky diaphragm appear dark, fogged, and often are nondiagnostic. Although a portable Potter-Bucky diaphragm is available for bedside roentgenography, this is impractical for routine urological investigation as it will only accommodate cassettes up to 10 by 12 inches in size. In an attempt to obtain diagnostic bedside films, a Lysholm grid was placed directly on top of a standard 14 by 17 inch cassette and exposures were made with the portable x-ray unit. This technique was employed in a series of 38 severely injured patients with eminently satisfactory roentgen results.

The Lysholm grid is, in effect, a stationary Potter-Bucky diaphragm and is used to reduce the fogging effects of secondary radiation. The scatter restraining efficiency of the Lysholm grid is equal, at least, to that of the moving Bucky. Two types of grids are obtainable: (1) the parallel or unfocused grid in which the lead strips are all laid parallel to each other and perpendicular to the surface of the grid, and (2) the focused or aligned grid, in which the strips are parallel at the center but angulated more and more as they approach the outer edge to align them with the direction of the primary beam. Flat Potter-Bucky diaphragms have this identical arrangement of lead strips. The target-film distance for the various available grids varies between 28 and 40 inches. Information concerning this is supplied by the manufacturers for each type of grid. The exposure time is approximately the same as with the moving Bucky diaphragm. For best results the tube should be perpendicular to the grid and centered with respect to both grid and film. Any tilt or shift must be parallel to the grid strips.

The grid is available for bedside use as a Lysholm wafer grid and as a Camp grid-front

From the Urological Service, Beekman-Downtown Hospital, New York.

Fig. 1. The technique for bedside x-ray examination is simple of execution. A patient who has sustained a fracture of the pelvis and spine is shown here being subjected to excretory urography. No discomfort or harmful effects to the patient result from this procedure.

cassette. Each type is obtainable in sizes ranging from 5 by 7 inches to 14 by 17 inches, although we have limited ourselves almost entirely to the latter size for routine use. The wafer grid, light in weight and approximately 2 millimeters thick, is placed directly on top of a standard cassette underneath the patient. If this grid is employed, we have preferred the focused type which has a target-film distance of 36 inches. The Camp grid-front cassette is a standard cassette into which a protected Lysholm grid has been mounted in place of the usual bakelite front. The grid in this cassette is prismatically focused at 28 inches target-film distance. We have found the Lysholm wafer grid and the Camp grid-front cassette to be equally effective in producing diagnostic roentgenograms. Although the former is more economical to purchase and less time consuming to use, we have preferred the Camp cassette since it is less vulnerable under conditions of bedside roentgenographic examination.

We have also found the cassette tunnel to be of considerable aid in bedside roentgen examination. It is inserted underneath the patient at the site to be roentgenographed and is removed at the conclusion of the roentgenological studies. The tunnel is of plywood construction and is reinforced at its bottom so that the mattress will not sag when the patient lies upon it. A slot at one end of the tunnel facilitates the handling of the Lysholm wafer grid on top of a standard cassette, or of the Camp grid-front cassette, both of which are easily and quickly changed after each exposure. The over-all thickness of the cassette tunnel has been kept to a minimum so that when it is placed on the bed, there is no discomfort to the patient. Its use does away with the necessity of lifting the patient up after each exposure in order to change the Camp grid-front cassette or the standard cassette and its overlying grid. Movement of the patient is thus reduced to a minimum.

The procedure for bedside x-ray examination as used by us is simple of execution (Fig. 1).

1. The cassette tunnel is positioned under the patient at the site to be roentgenographed.
2. A Lysholm wafer grid is placed over a standard cassette or a Camp grid-front cassette is inserted into the cassette tunnel and changed after each exposure.
3. The portable x-ray unit is positioned so that the target-film distance equals that given by the manufacturer for the particular grid used. The exposure time is approximately the same as with the moving Bucky diaphragm. (Our unit was 30 milliamperes and exposure time for an average subject was 3 seconds.)
4. Roentgenograms of the chest, skull, pelvis, abdomen, and long bones are taken as indicated.
5. Intravenous pyelograms, retrograde cystograms, or retrograde pyelographic exposures are then done in the conventional manner.

The decision as to whether to do an excretory pyelogram or a retrograde cystogram will depend on the presenting physical signs in the opinion of the surgeon or the urologist. Following an injury that may in any manner conceivably involve the genitourinary system, our routine has been as follows:

1. A catheter is passed to the bladder.

TABLE I.—SUMMARY OF UROLOGICAL PROCEDURES AND RESULTS IN 38 PATIENTS INVESTIGATED AT THE BEDSIDE

| | No. Cases |
|---|---|
| Harmful effects to patient | 0 |
| Excretory urography | 34 |
| Successful pyelograms; first attempt | 26 |
| Repeat pyelograms of those unsuccessful on first attempt; successful repeats | 4 |
| Diagnostic and satisfactory pyelograms in series | 27 |
| Diagnostic excretory cystograms in series | 28 |
| Patients in clinical shock (8); diagnostic and satisfactory intravenous pyelograms | 8 |
| Retrograde cystography | 16 |
| Diagnostic retrograde cystograms | 15 |
| (One patient with a normal appearing cystogram was explored because of increasing clinical signs and found to have a ruptured bladder.) | |
| Cystoscopy and retrograde pyelography | 9 |
| Confirmed diagnosis as rupture of kidney | 2 |
| Established diagnosis as contusion of kidney in cases in which the excretory urograms failed to reveal excretion on the injured side | 2 |
| Established diagnosis as contusion of kidney in cases in which the excretory urogram and clinical picture suggested a rupture of the kidney | 1 |
| Established diagnosis of a nonfunctioning ectopic kidney | 1 |
| Confirmed the presence of an impacted ureteral calculus | 1 |
| Confirmed the presence of a nonfunctioning, poorly draining, infected and hydronephrotic kidney | 1 |
| Indwelling ureteral catheter drainage | 4 |

3. The catheter is clamped and excretory urography performed. Late films at 60 and possibly 90 minutes are taken of the bladder in order to obtain a satisfactory cystogram.

4. If the excretory cystogram is unsatisfactory or suggestive of extravasation, the catheter is unclamped and retrograde cystography done.

4. The catheter is then withdrawn to just below the vesical neck and retrograde injection done.

5. If the catheter cannot be passed to the bladder, a urethrogram is obtained at the conclusion of the intravenous pyelography by the instillation of 20 cubic centimeters of a 10 per cent solution of the contrast substance.

Table I is a summary of the urological x-ray procedures performed at the bedside in 38 patients. There were no harmful effects as a result of these manipulations to any of the individuals in this series. Because of the fact that the reported experimental and clinical studies suggest that the best pyelograms are obtained immediately after the injury (3, 5, 7, 10), excretory urography was performed in 34 individuals soon after their admission to the hospital. This included 8 patients in clinical shock with a blood pressure between 68 to 76 millimeters of mercury systolic at the time the pyelograms were done. Most men do not advocate excretory urography if the patient is in shock, or if the blood pressure is below 80 millimeters of mercury systolic. It is generally agreed upon that the establishment of an anatomicopathologic diagnosis of the genitourinary trauma should be deferred until the patient is out of shock (13). However, occasionally, one may encounter patients who fail to rally despite adequate supportive and replacement therapy. Experience has taught me that in these instances an early accurate diagnosis

Fig. 2. Female, aged 50 years, was bleeding profusely from the urinary tract following an automobile accident. She was in clinical shock and failed to rally despite adequate supportive therapy. Her blood pressure was 68/50. Excretory urography discloses no excretion of the contrast substance from the left side in which area there is a large mass with obliteration of the psoas shadow. Nephrectomy performed with a great deal of assurance that she had a normal right kidney.

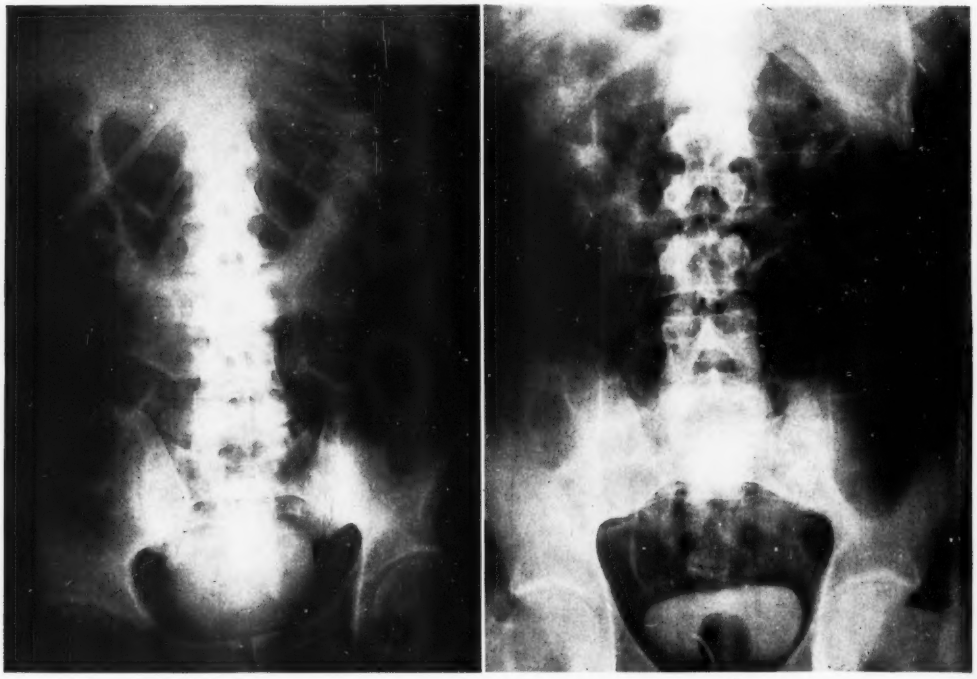

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Fig. 3. a and b, Two patients who had sustained a renal injury were bleeding profusely from the urinary tract. Excretory urography was performed at the bedside soon after admission to the hospital. Satisfactory and diagnostic pyelograms were obtained on the first attempt. In each case, the traumatized kidney was considered to be contused on the basis of these normal pyelograms, and the patients were treated conservatively.

and the necessary emergent operative intervention with multiple blood transfusions may, at times, be life saving (1, 5). The decided value of excretory urography at the bedside while the patient is being treated for shock was demonstrated in these 8 cases in each of which excellent pyelograms were obtained. Illustrative of these conclusions is the following case (Fig. 2):

A female, aged 50 years, was admitted to the hospital after being injured in an automobile accident. She was in clinical shock with a blood pressure of 68/50; the pulse was 142. Physical examination revealed a large tender mass in the left loin with crepitus of the eleventh and twelfth ribs in the mid-axillary line. Catheterization disclosed a grossly bloody urine with numerous blood clots. Despite the administration of 1,000 cubic centimeters of plasma and 1,500 cubic centimeters of blood, the clinical condition appeared to worsen. The mass in the left loin visibly increased in size and profuse urinary bleeding continued notwithstanding continued irrigation of the urethral catheter. It was quite evident to us that emergency operative interference would be necessary. Bedside x-ray studies revealed a fracture of the left eleventh and twelfth ribs and of the left second lumbar transverse process. The pelvic bones were intact. Excretory urography revealed excellent excretion from the right side which was considered normal; no excretion of the contrast substance was seen on the left, even on the late films. A large mass with obliteration of the psoas shadow was easily discerned on this side. With the aid of multiple transfusions during and after operation, a left nephrectomy was easily performed with a great deal of assurance that she had a normal right kidney.

TABLE II.—DIAGNOSES IN 38 PATIENTS EXAMINED AT THE BEDSIDE

| | No. Cases |
|---|---|
| **Surgical diagnosis** | |
| Shock on admission | 14 |
| Fractures of: | |
| Ribs | 19 |
| Femur | 15 |
| Pelvis | 13 |
| Transverse processes of vertebrae | 12 |
| Sacrum | 4 |
| Vertebrae | 4 |
| Humerus | 4 |
| Skull | 4 |
| Wrist | 2 |
| Ankle | 2 |
| Nose | 2 |
| Clavicle | 1 |
| Sternum | 1 |
| Separation of symphysis | 5 |
| Pneumothorax | 4 |
| Gas bacillus infection | 3 |
| Crushed chest | 3 |
| Laceration of brain | 3 |
| Concussion of brain | 3 |
| Mediastinal shift | 3 |
| Avulsion of perineum | 3 |
| Avulsion of rectal sphincter | 3 |
| Perivesical hematoma | 3 |
| Laceration of lung | 2 |
| Laceration of omentum | 2 |
| Contusion of spleen | 2 |
| Rupture of rectus muscle | 1 |
| Laceration of internal pudenal artery | 1 |
| **Urological diagnosis** | |
| Contusion of kidney | 12 |
| Rupture of bladder | 5 |
| Rupture of kidney | 4 |
| Rupture of urethra | 4 |
| Contusion of bladder | 2 |
| Laceration of urethra | 2 |
| Benign prostatic hypertrophy | 8 |
| Neurogenic bladder | 5 |
| Renal calculus | 3 |
| Calculous pyonephrosis | 2 |
| Nephroptosis, infected hydronephrosis | 2 |
| Avulsion of scrotum | 2 |
| Ectopic kidney | 1 |
| Horseshoe kidney | 1 |
| Impacted ureteral calculus | 1 |

In this group of 8 patients on whom excretory urograms were done while they were in shock, no harmful effects were noted by either the administration of the contrast material or the performance of the intravenous pyelograms.

Satisfactory excretory urograms (Fig. 3) were obtained on the first attempt in 26 of the 34 cases. The procedure was repeated in the 8 unsuccessful instances with more adequate dehydration and a series of pituitrin injections (12); 3 within several hours, and 5 on the following day. A satisfactory repeat was obtained in 4. Considered together, satisfactory and diagnostic pyelograms were seen in 27. Extravasation of the contrast substance diagnostic of a rupture of the kidney was obtained in 2 individuals (Fig. 4). Nine patients in this series were subsequently checked with cystoscopy and retrograde study at the bedside. Of these, 5 had been severely injured and were already in Russell traction at the time that urological opinion was requested because of the possibility of a traumatic lesion of the kidney. Although in 2 cases there was no excretion of the contrast substance from the af-

Fig. 4. The patient was admitted to the hospital soon after having been struck by a bus. The catheter urine was negative but there was a suggestive mass in the left loin. Excretory urography discloses a normal right kidney. On the left side, a large mass with an area of extravasated contrast material can be seen in the region of the lower pole. At operation, the lower half of the left kidney was avulsed. Nephrectomy was performed with a good result.

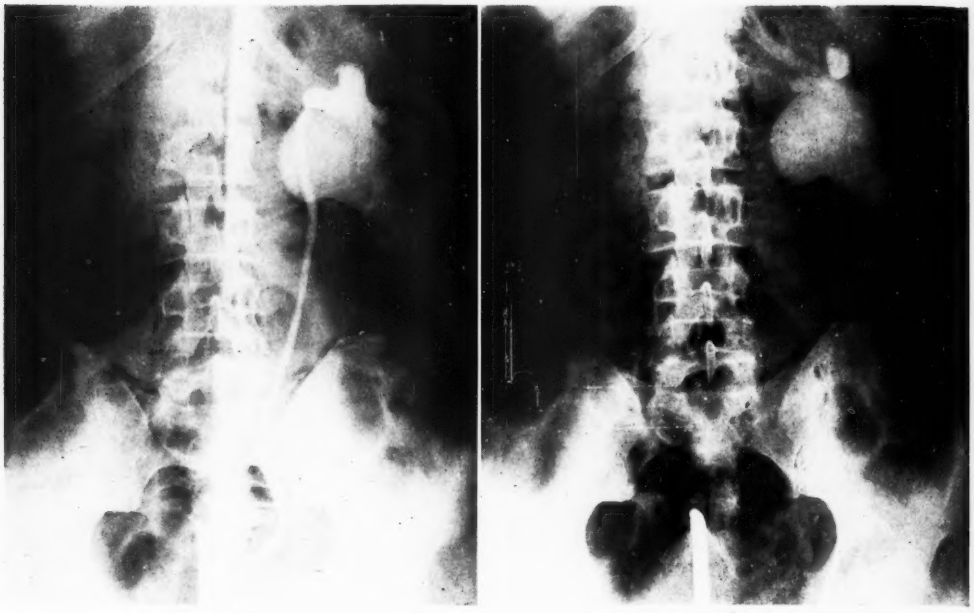

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Fig. 5. The patient had sustained a fracture of the femur in an automobile accident. Soon after he was put up in Russell traction, it was noted that he had a grossly bloody urine. Excretory urography on 2 occasions revealed a normal right urinary tract, and indefinite excretion from the left kidney. Because of persistent pain in the left loin, a rising temperature with chills, cystoscopy and retrograde pyelography were performed at the bedside. a, A left retrograde pyelogram discloses a dilated renal pelvis with a large area of extravasation in the region of the lower pole. b, A trapping film taken at the end of 10 minutes reveals an identical picture. None of the contrast material has drained from the kidney. At operation, the renal capsule was found to be intact. The lower pole of the kidney was split in half. The upper half was necrotic. Nephrectomy performed with a good result.

fected side and the clinical picture suggested a grave traumatic lesion, a retrograde pyelogram disclosed an intact, normal kidney in each. Retrograde study in the remaining 3 confirmed a diagnosis of rupture of the kidney in one, established the diagnosis as a true rupture of the kidney in another in whom the excretory urograms were unsatisfactory (Fig. 5), and indicated that the kidney of the fifth patient to be cystoscoped was merely contused although the excretory pyelograms and clinical picture suggested extravasation. These 5 cases demonstrated that when indicated and feasible, cystoscopy and retrograde pyelography may be done at the bedside with a minimum of discomfort to the patient. The knowledge obtained from this additional study is a further aid in the urological management of this group of patients (6, 9).

Diagnostic excretory cystograms were obtained in 30. Retrograde cystography was performed 16 times: in 6, because of an initial unsatisfactory excretory cystogram; in another 6 patients, because the clinical picture was strongly suggestive of a possible ruptured bladder although the excretory cystogram was satisfactory and disclosed no extravasation; and in 4 instances as a primary procedure in which no intravenous urography had been undertaken. Diagnostic retrograde cystograms were obtained in 15 of the 16 attempts (Fig. 6). The case in error occurred in a patient who, although he had a normal cystogram, was finally explored because of increasing physical signs and a deterioration in the clinical picture. At operation, a ruptured bladder with a moderate amount of extravasated urine was found in the retroperitoneal space. A rent

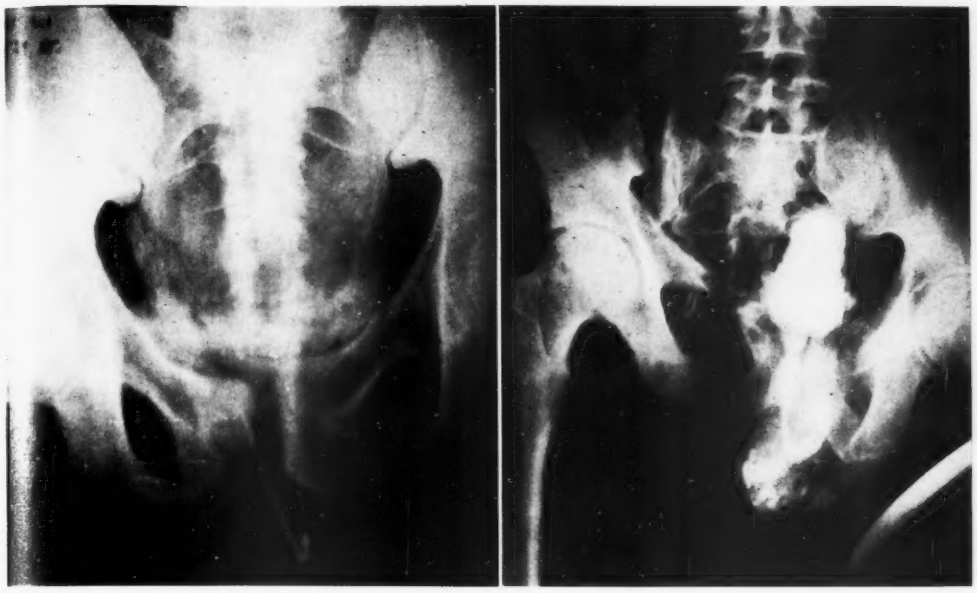

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Fig. 6. Satisfactory and diagnostic retrograde cystograms which were obtained in 2 cases of fracture of the pelvis. a, Extraperitoneal rupture of the bladder with "cloud-burst" type of extravasation. b, "Reverse tear-drop" type of bladder which was due to extraperitoneal rupture of the bladder.

in the lateral wall of the bladder was covered by adherent blood clot.

Although the retrograde cystograms were much more satisfactory and diagnostic as a group than the cystograms obtained by excretion urography (4, 9), one might be tempted to limit himself to retrograde cystography in cases of bony pelvic injury or in those instances in which the clinical evidence suggests a possible rupture of the bladder or the urethra. Experience has taught me, however, that it is much more judicious to adhere to the routine that I previously set forth; namely, first, to do an intravenous pyelographic series with late films of the bladder, and second, a retrograde cystogram, if indicated, at the conclusion of the excretory pyelograms. This routine gives us valuable information concerning the upper tracts and at times, one may be able to demonstrate extravasation from the bladder without resorting to retrograde injection (Fig. 7). In addition, one may be able, as was found in 1 of our cases, to find evidence for both a ruptured kidney and bladder in the same patient by the intravenous urograms.

The surgical and urological diagnoses in this series of 38 patients are enumerated in Table II. This indicates the advisability of a close degree of co-operation between the surgeon and urologist in the investigation and management of the severely injured patient. The technique of bedside x-ray examination as described in this paper should not be limited to a study of the urinary tract alone. We have found the procedure to be of immeasurable value in evaluating the various associated injuries that may be present. Roentgen studies of the abdomen for free air under the diaphragm, of the skull, chest, pelvis, and long bones may be accomplished easily and quickly by the use of the Lysholm grid; the films are highly satisfactory and diagnostic (Fig. 8). Follow-up roentgenograms at periodic intervals while the patient is bedridden or in traction will indicate the degree of healing of the bony lesions.

Fig. 7. Male, 22 years of age, injured in a motorcycle accident had sustained a fracture of the pelvis. He was able to void and had a grossly clear urine. Marked abdominal rigidity and tenderness present. Excretory urography performed. The upper urinary tracts were normal. A late film (60 minutes) of the bladder in the pyelographic series discloses a large area of extravasation. At operation, an extraperitoneal rent of the bladder was found and suture was performed.

Fig. 8. A male, 12 years of age, had sustained a fracture of the pelvis while sleigh-riding. Although the excretory urograms disclosed a laceration of the right kidney, he was thought to have an associated intra-abdominal lesion because of marked abdominal distention, and increasing abdominal rigidity and tenderness. A simple abdominal film reveals no free air. The bowel shows a diffuse generalized dilatation with no evidence for fluid levels. The abdominal signs seemed to be reflexly produced by injured right kidney.

A review of the urological diagnoses in this series (Table II) discloses that in 13 or one third of the patients, a serious traumatic urinary tract lesion was found, necessitating open surgical intervention. I believe that the procedure of bedside urological x-ray investigation was a life saving measure in several of these cases. The clinical evidence and physical signs were confusing in these instances and the only indication as to the seriousness of the injury was the information obtained from this study. No harmful effects were noted in any of these patients as a result of the procedure. The knowledge gained from this technique was immeasurable. If no serious urinary tract lesion is demonstrated one may treat such a case conservatively with a great deal of assurance that no operative intervention is indicated. If, on the other hand, rupture of the kidney or the bladder is found, one may institute the necessary surgery at the propitious time.

As a result of the bedside roentgen investigation, urological pathology unrelated to the trauma may be unearthed in some instances and proper therapy undertaken as indicated. Of interest in this series was the finding that 16 patients went into acute urinary retention soon after admission to the hospital. Five were found to have a neurogenic bladder due to an injury of the spine or sacrum. In 3 others, no pathology was discerned and the urinary retention was undoubtedly related to their being put to bed. Seven of these patients were treated with an indwelling urethral catheter. The eighth patient had re-

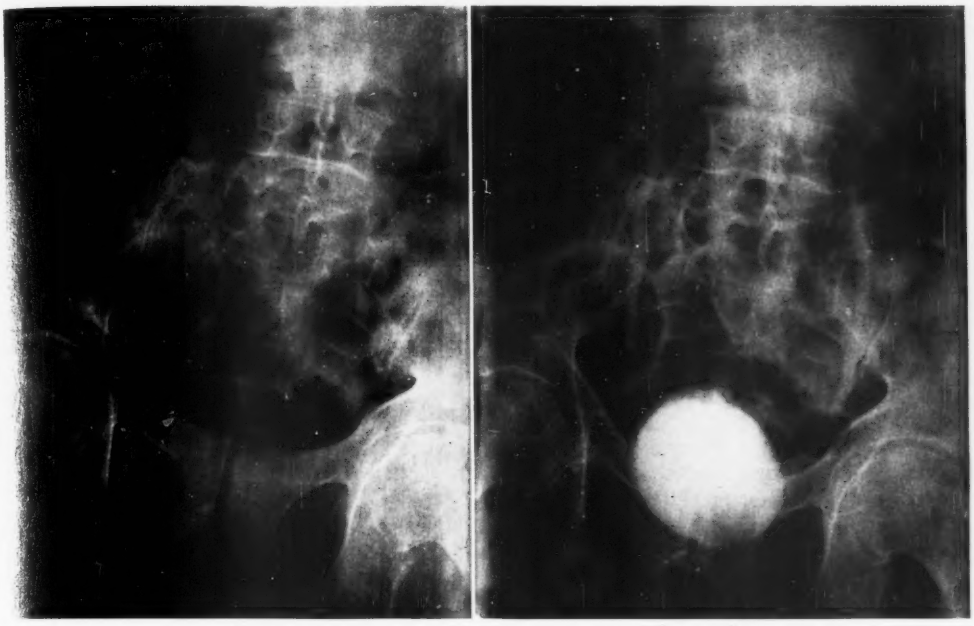

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Fig. 9. Male, 71 years of age, developed urinary retention 5 weeks after being put up in Russell traction for a fracture of the neck of the femur. Despite indwelling urethral catheter drainage, he had a daily chill and temperature elevation to 105 degrees. Retrograde cystogram reveals marked reflux up both ureters. Suprapubic cystotomy was performed resulting in cessation of his symptoms.

repeated chills with temperature elevation to 104 degrees. Retrograde cystogram revealed marked reflux up both ureters (Fig. 9). Suprapubic cystotomy was then performed with cessation of his symptoms. A diagnosis of benign prostatic hypertrophy was made in the remaining 8 individuals on the basis of their clinical history and cystographic x-ray findings. Two of these patients were treated with an indwelling urethral catheter. The remaining 6 were subjected to a preliminary suprapubic cystotomy, followed later by a suprapubic prostatectomy or transurethral resection when the individual was out of Russell traction or had recovered sufficiently from his surgical trauma.

Patients who have sustained fractures of the lower extremities may, at some time during their prolonged period of immobilization in skeletal traction, present symptoms of pain in the loin, chills, fever, pyuria, or hematuria necessitating urgent urological consultation. Instead of deferring urological roentgen investigation of these patients until they can be safely transported to the x-ray department, one may perform such studies at the bedside employing the technique described. In this series, by following the routine outlined, there were found 2 patients with an infected and hydronephrotic kidney, 2 with a calculous pyelonephrosis, and 1 with an impacted large low ureteral calculus. Relief of symptoms was accomplished in 4 instances by means of irrigation of an indwelling ureteral catheter put up at the time of cystoscopy. The other 2 patients were operated upon, a nephrectomy being done in one and a ureterolithotomy in the other.

## SUMMARY

A series of 38 severely injured patients whose general condition contraindicated movement to the x-ray department for roentgenological study were subjected to urological roentgen investigation at the bedside.

By using the portable x-ray unit and either a Lysholm grid placed over a standard cassette or a Camp grid-front cassette in a cassette tunnel positioned underneath the patient at the site to be x-rayed, the films were found to be extremely satisfactory and diagnostic. Although this study was principally concerned with investigation of the urinary tract, the method of bedside x-ray examination was also found to be of considerable value in the diagnosis of associated bony or visceral lesions.

The technique is simple of execution. No harmful effects were noted in any of these patients as a result of the procedure. On the other hand the benefits derived from the knowledge obtained by this study were immeasurable. By its routine use in this select group of individuals, it was possible to obtain an early and accurate anatomicopathologic diagnosis of the urinary tract trauma. This is a prerequisite in the evaluation of conservative versus operative intervention if we are to institute rational therapy in time for it to be of real value.

In addition, this method of examination was also found to be of considerable merit in patients without any urinary tract injury who might develop genitourinary symptoms while immobilized in surgical traction. Urological pathology unrelated to the surgical trauma may be unearthed for which conservative or operative treatment may be undertaken as indicated.

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# OBSERVATIONS ON THE USE OF AN ARTIFICIALLY INDUCED PROGESTATIONAL STATE AS A PREOPERATIVE ADJUNCT TO RADICAL PELVIC SURGERY

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FOLLOWING the administration of large amounts of progesterone to patients with epidermoid carcinoma of the cervix uteri, certain effects were noted in the organs and tissues of the pelvis which resembled, at the time of the surgical procedure, those of early pregnancy. As hysterectomy and other pelvic surgical measures are, technically, less difficult to perform in the gestational state, the use of progesterone as a preoperative adjunct to radical pelvic surgery might facilitate the surgical procedure and decrease the incidence of postoperative complications. This study was undertaken to evaluate this concept.

That surgical dissection is less difficult during pregnancy is one of the oldest recorded gynecologic observations. In 1897 Olshausen (cited by Cullen) recognized the favorable influence of pregnancy on pelvic surgery and reported on 25 cases of patients with carcinoma of the cervix who were treated by vaginal hysterectomy during the early months of pregnancy without a single fatality. He stated that "in pregnancy the vagina is more capacious, the tissues are soft and, on account of its increased elasticity, the uterus can be drawn much lower down than usual. As a result, one can reach lateral structures much farther out than would be possible under ordinary circumstances." He concluded that vaginal hysterectomy was the method which promised the best results in carcinoma of the cervix when surgical intervention was instituted during the early months of pregnancy.

One year later Fritsch (3) observed similar changes during pregnancy and reported a case in which total vaginal hysterectomy was performed at full term for treatment of carcinoma of the cervix.

In 1938, Chromé and Versini reviewed the changes occurring in the genital apparatus during pregnancy and labor and concluded that the peritoneum which covers the lower uterine segment is easily separable throughout when there is softening of the subperitoneal cellular tissue as a result of pregnancy.

Today, suprasymphyseal extraperitoneal cesarean section probably demonstrates better than any other common procedure the favorable influence of pregnancy on actual surgical technique. The favorable factors are: (1) increased vascularity; (2) edema of the subperitoneal areolar connective tissue which aids in dissection along tissue planes; (3) increased uterine mobility, which is due to softening of the uterine ligaments and which improves exposure. That these changes might be produced by progesterone is rational since they coincide in degree with the rate of growth of the corpus luteum during the first 3 months of pregnancy.

## MATERIALS AND METHODS

Eighteen patients with epidermoid carcinoma of the cervix uteri were treated with large doses of progesterone, followed by definitive pelvic surgery. The patients were selected without regard to their general physical condition, age, race, or nutritional status. All were hospitalized and, in all, the

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Fig. 1. Showing changes in a 65 year old patient after 12.5 grams of progesterone.

reports on the biopsies were positive for carcinoma. The stage of the disease was recorded according to the League of Nations classification. The cases were divided into two groups. In the initial 10 cases, 4 patients had recurrent carcinoma following irradiation therapy and were suitable only for radical palliative surgical care or for terminal care. In the last 8 cases, only those patients with clearly visible cervical lesions were selected in order to permit evaluation of the clinical effects of exogenous progesterone on epidermoid carcinoma of the cervix uteri. The results of this portion of the study have been reported elsewhere (5).

All of the patients received 250 milligrams of progesterone intramuscularly in 5 cubic centimeters of oil for varying periods of time prior to the surgical procedure, as indicated in Table I. The smallest amount of progesterone given was 400 milligrams administered over a period of 3 days, and the largest amount was 28.85 grams administered over a period of 113 days. The smallest amount was administered to a patient in whom local reactions developed at the injection sites and this necessitated discontinuance of therapy.

Prior to progesterone therapy, each patient had a general medical appraisal, including proctoscopic examination, cystoscopic examination and intravenous pyelography. In addition, when indicated, roentgen examination of the colon by barium enema and of the kidneys by retrograde pyelography was obtained. Blood transfusions were given when necessary to bring the blood count and plasma proteins to within normal limits. For 1 week prior to the scheduled surgical intervention each patient received 3 grams of sulfasuxidine every 4 hours. On the evening of the fourth preoperative day, 45 cubic centimeters of castor oil was given by mouth. For 3 days prior to operation, diet was restricted to clear liquids, and daily cleansing enemas were given. At the time of operation, sodium pentothal was used for induction and was followed by gas-oxygen-ether to insure surgical relaxation. The operative procedures employed were either: (1) radical hysterectomy, or (2) partial pelvic evisceration. The radical hysterectomy employed was the combination Wertheim hysterectomy and Taussig node dissection as described by Meigs. It entails the removal of all nodes from the common iliac, external iliac, and hypogastric arteries, the contents of the obturator fossae with exposure and preservation of the obturator nerve, and the removal of parametrial structures and upper vagina.

Pelvic evisceration includes the removal of the bladder and all or part of the vagina. The technique used is similar to that of Brunschwig (1, 2) and Marshall and his associates. However, in this series the rectum was preserved and the ureters were implanted into the rectosigmoid after complete mobilization of the uterus and bladder. The perineal wound was drained at the end of the perineal phase and a rectal tube was inserted and anchored in place by adhesive tape or skin sutures.

Postoperatively, constant gastric aspiration was maintained for at least 48 hours. At least 400,000 units of penicillin were administered daily for 5 days. Fluid balance was maintained. The rectal tube was removed in 5 to 7 days. Patency of the tube was assured by gentle daily irrigations with tap water. For 2 or 3 days postoperatively nothing was given by mouth. Thereafter fluids and diet were gradually increased as the patient's tolerance permitted. Activity and early ambulation were encouraged as soon as possible.

The surgical specimens were fixed in Bouin's solution and serial blocks were removed for histopathologic study. The lymph nodes were carefully identified, enumerated, fixed, and sectioned for microscopic study. The number of patients with positive lymph nodes, the location of residual carcinoma, and the type of endometrium have been summarized in Table I.

Quantitative estimation of the degree of response of pelvic viscera to the administration of progesterone based on objective findings at the time of the surgical procedure was graded from 1 to 3 plus. A 1 plus response indicated capillary injection and moderate hyperemia, with little or no tissue edema and softening. A 3 plus response represented the maximum degree of tissue edema, softening, ease of separation of tissue cleavage planes and surgical exposure encountered. The intermediate grade, 2 plus, represented changes between these extremes as interpreted at the time of the surgical intervention.

## RESULTS

The cases are summarized in Table I. In the group, 4 were classed as stage I; 5 as stage II; 5 as stage III; 2 as stage IV; and 2 as stage 0 (carcinoma in situ). The youngest patient was 31 years of age, the oldest was 65, and the average age for the entire series was 50. Ten patients (Cases 2, 3, 4, 6, 11, 13, 15, 16, 17, and 18) were treated by the radical hysterectomy with node dissection. Seven patients (Cases 1, 5, 8, 9, 10, 12, and 14) were treated by partial pelvic evisceration. One patient (Case 11) had the vena cava ligated at the time of the radical hysterectomy. One patient (Case 7) with carcinoma in situ had only a total hysterectomy. Four patients (Cases 1, 3, 6, and 10) had recurrent carcinoma following irradiation. Two of these were classed as stage II, 1 as stage III, and 1 as stage IV.

In the series, 13 patients (Cases 1, 2, 4, 5, 6, 7, 9, 10, 11, 12, 13, 16, 17) showed a 3 plus response; 4 patients (Cases 8, 14, 15, and 18) showed a 2 plus response; and 1 (Case 3) showed a 1 plus response. In the cases showing the maximum response, the results, as seen at the operating table were uniformly satisfactory. There was moderate hyperemia and congestion of the uterus and capillary injection of the tubes and broad ligaments (Fig. 1). The edema of the subperitoneal connective tissue produced a glistening mucus-like appearance best seen through the pelvic peritoneum over the iliac vessels. Capillary ooze, while present, was never troublesome.

Of the patients showing a 3 plus response 3 (Cases 1, 6, and 10) were in the elderly age category and had received previous irradiation. They received 1,200 milligrams in 12 days, 6,000 milligrams in 28 days, and 4,500 milligrams in 29 days, respectively.

Of the 4 patients (Cases 8, 14, 15, and 18) showing the 2 plus response, 1 had received the smallest total dose of the entire series (400 milligrams in 3 days), while the other 3 had received the 3 largest total dosages (28.85 grams in 113 days, 18.5 grams in 103 days, and 16.25 grams in 65 days).

The patient (Case 3) showing a 1 plus response exhibited a mild capillary injection, little tissue edema and no appreciable softening. Consequently, the progesterone effects in this case did not facilitate the surgery. This patient was a diabetic and had received extensive external and transvaginal roentgen therapy for a stage II lesion 2 years before operation. She received 2,100 milligrams of progesterone in 13 days, followed immediately by surgical intervention. This was the only patient in the series who had received transvaginal cone therapy.

The amount of progesterone administered to 2 of the 4 patients who had received pre-

vious irradiation was considerably smaller than in all subsequent cases and did not exceed a total dosage of 2,100 milligrams administered over a period of 13 days. Nevertheless, 1 of these (Case 1) showed a satisfactory response consisting of increased relaxation of the uterine supporting structures, demarcation of cleavage planes, and increased vascularity and edema of the subperitoneal areolar tissue.

Three patients (Cases 5, 10, and 14) had postoperative urinary tract complications following partial pelvic evisceration. In 1 (Case 5), pyelitis developed on the seventh postoperative day and failed to respond to intensive treatment with blood transfusions and antibiotic drugs. In spite of drainage of the infected kidney and the institution of an ileostomy, she died in uremia on the seventeenth postoperative day. One (Case 10) in addition to the pyelitis developed myocardial infarction. After a stormy course, she recovered. In the other (Case 14), a mild attack of pyelitis developed on the eleventh postoperative day. This responded readily to sulfadiazine therapy.

The second death (Case 12) occurred on the twenty-third postoperative day and was not satisfactorily explained at autopsy. Following an uneventful convalescence, she had been discharged from the hospital on the twentieth postoperative day. Two days later she was readmitted in a semistuporous condition and died within 24 hours. The 2 postoperative deaths, both in previously untreated patients and after the more radical type of surgical procedure for stage III lesions, constitute a mortality rate of 11 per cent for the entire series and 30 per cent for partial pelvic evisceration. In addition to the 2 postoperative deaths, 2 patients (Cases 6 and 8) died at 10 months and 9 months, respectively, from extensive metastases. The remaining 14 survivors are alive and well today, without evidence of disease. Sufficient time has not elapsed to predict the ultimate outcome.

There were 3 stump cases (Cases 5, 9, and 16) in the entire series. Of the surgical specimens from the remaining patients, 11 showed an atrophic, 3 a proliferative, and 1 a late secretory endometrium. The patient with the secretory type (Case 7) was a 32 year old negro woman with a carcinoma in situ who received 3,000 milligrams in 12 days. Of the patients showing an atrophic type of endometrium, 4 were in the menstruating age group and had received no irradiation therapy.

## DISCUSSION

While the number of patients is small, the results indicate that in some of the patients, clinical changes can be produced by the administration of progesterone. The degree of response does not seem to be closely correlated with the total dosage, duration of treatment, type of previous radiation therapy, or age of the patient.

One patient who received 1,200 milligrams in 12 days had a maximum response, while another who received 2,100 milligrams in 13 days showed no response, and a third who received 28.85 milligrams in 113 days showed only a weak response. In general, however, those patients receiving the larger doses showed a higher incidence and degree of favorable clinical response.

Among those who received previous irradiation therapy, the amount given varied. However, an impression was gained that the degree of response was influenced by the amount of radiation fibrosis which was present. This was most apparent in the 1 patient who had previously received intensive transvaginal roentgen therapy through an unscreened cone and had, at operation, the most marked radiation fibrosis of the pelvic structures. Although she received an adequate amount of progesterone, there was no clear evidence of any effect. However, the incidence of maximum response (3 plus) was the same (75 per cent) in the group which had received and that which had not received previous irradiation.

The fact that the 3 patients who received the 3 largest total amounts of progesterone showed no response suggests that there may be a maximum level beyond which an inhibition of response may occur.

The minimal amount of progesterone and duration of treatment necessary to produce

TABLE I.—SUMMARY OF CLINICAL DATA ON USE OF PROGESTERONE PREOPERATIVELY

| Case, color, age | Diagnosis | Operative risk | Previous treatment | Progesterone administered | Response | Surgical procedure | Complications | Surgical specimen |
|---|---|---|---|---|---|---|---|---|
| 1 M.M. wh. 62 | Epid. ca. stage III | Fair | Full course x-ray 3,340 mgm. hrs. radium | 1.2 gms. in 12 days | *** | 1–3–49. Radical with nodes, cystectomy vaginectomy, bilateral ureteral implants | None | Epid. ca. cervix and vagina, hemorrhagic and atrophic endometrium |
| 2 A.J. wh. 54 | Epid. ca. stage I | Good | None | 1.5 gms. in 10 days | *** | 2–18–49. Radical with nodes | None | Epid. ca in situ, mod. atrophic endometrium |
| 3 R.H. col. 41 | Stage II pos. smears after therapy | Diabetic | 8,600 x-ray intravaginally 12,000 r. externally | 2100 mgms. in 13 days | * | 3–21–49. Radical | None | Radiation reaction, atrophic endometrium |
| 4 L.K. wh. 36 | Epid. ca. stage I | Good | None | 2 gms. in 10 days | *** | 3–31–49. Radical with nodes | None | Epid.ca.pseudomucinous cystadenoma ovary, nodes negative, late proliferative endometrium |
| 5 A.P. col. 58 | Epid. ca. stage III | Poor—arteriosclerosis hydronephrosis, hydroureter, left | Subtotal hysterectomy 5–16–48 | 3.15 gms. in 21 days | *** | 4–4–49. Radical stump with nodes, cystectomy, vaginectomy, ureteral implant (1) and ligation (1) | Severe pyelonephritis, ileus, uremia, death | epid. ca., stump case |
| 6 E.M. col. 58 | Epid. ca. stage II | Poor—malnourished | Intracavitary radium in 1933 for profuse bleeding | 6 gms. in 28 days | *** | 5–2–49. Radical with nodes | None | Epid. ca, 15 nodes negative, atrophic endometrium |
| 7 B.P. col. 32 | Ca. in situ | Good | None | 3 gms. in 12 days | *** | 7–18–49. Total hysterectomy | None | Fibroids, endometriosis, late secretory endometrium |
| 8 E.S. wh. 34 | Epid. ca. stage IV | Poor—metastatic chest lesion | None | Discontinued after 400 mgms. because of severe reaction at site of injection | ** | 8–10–49. Radical with nodes, cystectomy, vaginectomy, bilateral ureteral implants | None | Epid. ca. 6 of 12 nodes positive, proliferative endometrium |
| 9 D.W. col. 53 | Epid. ca. stage III | Poor | Pelvic operation at 17 yrs. of age | 7.425 gms. in 61 days | *** | 9–9–49. Radical stump with nodes, cystectomy, vaginectomy, bilateral ureteral implants | None | Epid. ca., stump case |
| 10 J.V. col. 61 | Epid. ca. stage IV | Poor—severe anemia, arteriosclerosis, malnutrition | Dec. 1947—7,680 mgm. hrs. of radium to cervix. Jan. 1948—10,000 r. deep x-ray | 4.5 gms. in 29 days | *** | 9–23–49. Radical with nodes, cystectomy vaginectomy, bilateral ureteral implants | Severe myocardial infarct and pyelitis | Radiation necrosis of bladder, atrophic endometrium |
| 11 Z.S. col. 65 | Epid. ca. stage II | Poor—arteriosclerosis, 2 episodes of pulmonary infarction | None | 12.5 gms. in 50 days | *** | 11–11–49. Radical with nodes, vena cava ligation | None | Epid. ca., atrophic endometrium |
| 12 M.P. col. 61 | Epid. ca. stage III | Fair | None | 16 gms. in 64 days | *** | 12–2–49. Radical with nodes, cystectomy, vaginectomy, bilateral ureteral implants | Died 12–25–49. Not satisfactorily explained at autopsy | Epid. ca., hemorrhagic and atrophic endometrium |
| 13 E.P. wh. 31 | Epid. ca. stage I | Good | None | 7.25 gms. in 31 days | *** | 3–21–50 Radical with nodes | None | Ca. in situ, proliferative endometrium |
| 14 G.H. wh. 56 | Epid. ca. stage III | Fair—obesity | 1926—bilateral oophorectomy | 28.85 gms. in 113 days | ** | 4–13–50. Radical with nodes, cystectomy, vaginectomy, bilateral ureteral implants | Mild attacks of pyelitis | Epid. ca. of cervix, corpus, and bladder, 2 of 17 nodes positive, atrophic endometrium |
| 15 G.McN. wh. 59 | Ca. in situ | Fair | None | 18.5 gms. in 103 days | ** | 6–2–50. Radical with nodes | None | Chronic cervicitis, atrophic endometrium |
| 16 M.W. col. 36 | Epid. ca. stage I | Good | 1946—bilateral oophorectomy | 7.25 gms. in 31 days | *** | 6–7–50. Radical with nodes | None | Epid. ca., negative nodes, stump case |
| 17 M.W. col. 35 | Epid. ca. stage II | Good | None | 16.25 gms. in 65 days | *** | 6–9–50. Radical with nodes | None | Epid. ca., negative nodes, atrophic endometrium |
| 18 E.G. wh. 65 | Epid. ca. stage II | Good | None | 16.25 gms. in 65 days | ** | 6–14–50. Radical with nodes | None | Epid. ca., negative nodes, atrophic endometrium |

a satisfactory clinical response cannot be stated. From the results obtained in this series, 1,200 milligrams in 12 days is the smallest amount which produced a satisfactory response.

In the 13 patients (72 per cent) who showed a 3 plus gravidoid response, the clinical changes did not approach in degree those associated with an early pregnancy but were sufficiently marked to be considered surgically favorable. The subperitoneal edema aided dissection along cleavage planes and the relaxation of the supporting structures permitted easier mobilization of the pelvic viscera. These results alone are sufficiently encouraging to warrant further studies.

Routine histopathologic studies on the surgical specimens failed to show a morphologic basis for the tissue changes previously described and attributed to the use of the steroid. However, the excised uteri of 4 of the 5 patients in the menstruating age group, all previously untreated by irradiation, contained atrophic endometria. The endometrial pattern was described by the pathologist as similar to that seen during "early menopause." This would suggest that the continuous administration of large amounts of progesterone may lead to atrophy of the endometrium. Similar changes in the endometrium of the estrogen-progesterone treated ovariectomized monkey following the prolonged use of the steroids have been reported (6).

The urinary excretion levels for pregnandiol glucuronide, which were determined and found to be within normal limits in every case in this series, have been reported in a separate publication (6). These findings, while indicating the patient's ability to metabolize exogenous progesterone, were of little value in predicting the clinical response since the percentile recovery of the glucuronide was not materially influenced by the dosage and the duration of therapy.

With the ever increasing scope of surgery in the treatment of cancer, particularly in the advanced cases and those recurrent after irradiation, any method which aids the difficult task of the surgeon merits careful consideration. The degree of surgical ease and freedom which can be obtained by the use of large doses of progesterone preoperatively is a step in this direction.

## SUMMARY

1. The results of the preoperative administration of large doses of progesterone to 18 patients with epidermoid carcinoma of the cervix uteri (including 2 cases of carcinoma in situ) are presented.

2. In 75 per cent of the cases at the time of operation varying degrees of gross changes were demonstrated in the organs and tissues of the pelvis, not unlike those of early pregnancy. These changes were designated as a gravidoid response.

3. The degree of response revealed wide individual variations and was not directly related to dosage, age, and the manner and method of application of previous irradiation.

4. The response facilitated the surgery and may be a factor in minimizing complications. Therefore, large doses of progesterone preoperatively are a valuable surgical adjunct to the performance of radical pelvic surgery.

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# UROLOGIC PROCEDURES EMPLOYED IN THE DIAGNOSIS OF URINARY-VAGINAL FISTULAS

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URINARY incontinence following gynecologic or obstetric operations is extremely distressing to both patient and surgeon. In most instances the urinary leakage results from a fistulous connection between a portion of the urinary tract and the vagina. Too frequently hasty repair of the fistula is attempted, without adequate urologic study, in an effort to eradicate the patient's incontinence and to allay the chagrin of both patient and surgeon. Successful repair of urinary fistula requires thorough and precise urologic study prior to operation. The purpose of this paper is to describe the urologic methods and procedures employed in such study.

## VARIETIES AND CAUSES

Usually, urinary-vaginal fistulas are vesicovaginal or ureterovaginal in nature. Other varieties of fistulas, such as vesicocervicalvaginal, ureterotubal, ureterouterine, and combinations of these, occur and the skill of the urologist may be taxed to make a precise diagnosis before repair is attempted.

The majority of the fistulas here considered result from obstetric or gynecologic trauma. They have developed following well conceived and well executed surgical procedures carried out by competent surgeons.

Various surgical procedures may give rise to fistulas. Hysterectomy, either vaginal or abdominal, is the most common cause of vesicovaginal or ureterovaginal fistulas. In their course through the parametrium the ureters lie close to the uterus. As they leave the parametrium the ureters approach to within 1 inch (2.5 cm.) of the lateral fornix of the vagina. These anatomic relations explain the ease with which the ureters may be damaged. Furthermore, the pathologic process which necessitates the hysterectomy may extensively alter the anatomic relations. The close proximity of the uterus and bladder likewise accounts for the ease with which the bladder may be torn, cut, or damaged by suture in the course of hysterectomy. Less frequently, plastic procedures applied to the vagina, vesical neck, or urethra may result in fistulas.

Vesicovaginal fistulas following childbirth usually are attributable to trauma from obstetric forceps or to other maneuvers of the obstetrician during a difficult delivery.

## DIAGNOSIS

The problems involved in diagnosis can best be considered by describing the steps taken by a urologist when confronted with a patient who is suspected of having a urinary fistula. He must first establish that the fluid which is escaping is urine. Not infrequently vaginal discharge of patients who have undergone recent vaginal operative procedures is mistaken for urine. This question usually can be settled by visual examination of the vagina. If doubt remains, a pack can be placed in the vagina and 5 cubic centimeters of indigo carmine administered intravenously. The drug is excreted in the urinary tract and the pack will be stained bluish-green if a urinary fistula is present.

Between them, the urologist and the patient should arrive at exact description of the nature of the leakage. This may suggest the type of fistula. Thus, vesicovaginal fistulas usually result in continuous escape of urine into the vagina, without voluntary urination. In most instances, insufficient urine is contained in the bladder to produce the sensation of the necessity to urinate. If the fistula is small, the patient may be able to void small amounts of urine in spite of its constant escape into the vagina. If the fistula is high on the lateral or posterior vesical wall, the patient may be continent while supine. Associated cystitis may cause distress in the suprapubic area.

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Certainly, the urologist should elicit a complete list of the symptoms. Patients who have ureterovaginal fistulas usually will recall that during surgical convalescence they experienced pain in the flank, and possibly chills and fever, prior to the onset of urinary incontinence. In spite of constant leakage of urine into the vagina, these patients experience normal vesical sensations and are able to urinate normally. The symptoms noted by patients with urethrovaginal fistulas vary with the site of the fistula. If the fistula is close to the vesical neck, the symptoms resemble those of vesicovaginal fistula. Fistulas in the distal portion of the urethra result in escape of urine into the vagina only during urination.

*Roentgenologic examination.* Excretory urography should be carried out in all cases in which urinary fistula is suspected. This examination may suggest the correct diagnosis and will depict the condition of the upper part of the urinary tract.

In cases of vesicovaginal fistula the upper part of the urinary tract will be normal unless antecedent urologic disease has been present. It is possible, however, that a ureteral orifice may be compromised by an inflammatory reaction secondary to a vesicovaginal fistula in its immediate vicinity; in such instances, hydroureter and hydronephrosis may occur. Ureterovaginal fistulas, on the other hand, usually are associated with abnormality of the upper part of the urinary tract. Excretory urography generally will disclose unilateral hydroureter and hydronephrosis of varying degree. Rarely, one kidney will not be visualized and, equally rarely, the upper part of the urinary tract will appear normal. Urethrovaginal fistulas are not associated with changes in the upper part of the urinary tract.

In the presence of any type of fistula evidence of a pool of opaque medium in the vagina may be seen; however, the affected kidney must retain function for this to be true of the ureterovaginal group.

*Cystoscopic examination.* Cystoscopic examination is undertaken following excretory urography. If a vesicovaginal fistula is present it usually can be visualized in the base, or posterior wall, of the bladder. If a fistula is detected, its size and position should be noted; the relationship between the fistula, on the one hand, and the trigone and ureteral orifices, on the other hand, should be determined. The presence of multiple vesicovaginal fistulas and the degree of infection of the bladder should be noted. If a vesicovaginal fistula is large, cystoscopy may be unsatisfactory because of escape of the irrigating fluid. If the fistula is single and small, a guide thread passed through the fistula may make it more easily found at the time of surgical repair. For this purpose a No. 3 or No. 4 F. ureteral catheter is passed through the fistula into the vagina at the time of cystoscopy. A piece of surgical silk, commonly called "fishline," is tied to the end of the catheter and the catheter is withdrawn from the vagina until the fishline appears. The catheter is discarded and the ends of the fishline are tied together. This serves as an excellent guide at the time of surgical repair. A lead shot may be attached to the fishline and directed into the bladder up against the fistula. Tension on the vaginal loop of the fishline will draw the fistula into the surgical field.

In cases of ureterovaginal fistula the bladder will appear normal. Ejaculation of urine from the involved ureter may be absent or weak. Obstruction will be encountered in the ureter during the passage of a ureteral catheter; usually the obstruction is impassable.

*Vaginal examination.* Careful examination of the vagina is necessary in the presence either of vesicovaginal or of ureterovaginal fistulas. By reason of its size or position, it may be impossible to detect a vesicovaginal fistula on cystoscopic examination. Vaginal examination with the aid of a light-carrying speculum is helpful. In such instances, water may be instilled into the bladder and the vagina searched for the site of its escape. If this is unsuccessful, the fistula may be detected by using a dye such as indigo carmine instead of water. When the fistula is found, a catheter may be passed through it from the vagina into the bladder. For this purpose a curved director is helpful. A guide thread is tied to the end of the catheter, cystoscopy is performed, and the catheter is drawn out of the bladder until the guide thread appears. The guide thread is then tied in place. The

relationships of the fistula are noted at the time of cystoscopy.

Detection of the vaginal opening of a ureterovaginal fistula frequently is aided by intravenous administration of indigo carmine. At times it may be possible to pass a catheter through the fistula by employing the curved director. The correct diagnosis is established by securing a pyelogram.

### THE UROLOGIST'S ROLE

Frequently it is impossible to predict whether a ureter will be traumatized in the course of a proposed surgical operation. If, however, there is any reason to suspect that such trauma may occur, the urologist should be requested to place a catheter in each ureter prior to the operation. By this means the ureters can be more easily identified and avoided and the development of fistulas thus obviated.

The urologic surgeon, the general surgeon, and the gynecologic surgeon each claims that repair of urinary fistulas is within his province. It is not the purpose in this paper to enter into medical polemics. However, if it is the intention of a surgeon, other than a urologic surgeon, to repair a urinary fistula, he should request the help of a urologist. For the surgeon must know, before he begins to operate, whether a fistula is vesicovaginal, ureterovaginal, or of some other variety. He must know also its exact nature and the nature of related conditions, as will appear.

*Vesicovaginal fistulas.* It is imperative that, in a case of vesicovaginal fistula, the surgeon be informed of the exact number, size, and position of the fistulas before he attempts repair. Treatment of associated cystitis may be necessary to decrease infection in the tissues which are to be employed in repair. If a vesicovaginal fistula is small, cystoscopic fulguration and drainage by urethral catheter, while the patient is on a Bradford frame, may result in its closure. The value of preliminary insertion of a fishline has been explained.

If the fistula is situated in the immediate vicinity of the ureteral orifice it is possible for the latter to be injured in the course of surgical repair. In such instances a catheter should be inserted into the ureter prior to operation in order to provide ready identification of the ureter.

*Ureterovaginal fistula.* The method of dealing with ureterovaginal fistula will depend on the results of urologic study. The urologist can estimate the functional capacity and degree of infection of the ipsilateral kidney and the condition of the opposite kidney. These studies will determine whether conservative treatment is advisable or whether a radical procedure is necessary. If the ipsilateral kidney is in good condition, it may be possible to pass a ureteral catheter to the renal pelvis. The catheter is left indwelling for 10 to 14 days and, in some instances, closure of the fistula will result. Urologic investigation may disclose that the kidney is damaged slightly or not at all, and that reimplantation of the ureter into the bladder is advisable. On the other hand, severe renal damage would indicate nephrectomy.

### SUMMARY

Failures in repair of urinary-vaginal fistulas frequently are attributable to incomplete urologic study and treatment before operation. Employment of various urologic methods and of other adjunctive procedures facilitates reparative surgical measures.

# CHANGES IN BLOOD VOLUME FOLLOWING ADMINISTRATION OF DEXTRAN—DETERMINED BY $P^{32}$ LABELED RED CELLS

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BECAUSE of the widespread interest in the use of macromolecular substances as plasma volume expanders, the present study was undertaken to determine the changes in the whole blood and plasma volumes following the administration of 500 cubic centimeters of 6 per cent dextran (C.S.C.) in normal saline. Turner and his associates observed an average increase of 370 cubic centimeters in plasma volume 24 hours after the intravenous injection of 500 cubic centimeters of 6 per cent dextran in normal saline.

## METHODS

Red blood cells were labeled with $P^{32}$ and the initial blood volume determined by the method of Hevesy and Zerahn as modified in this laboratory (1). At intervals of approximately ¼, ¾, 3, 5, and 22 hours, blood samples were withdrawn and the $P^{32}$ activity determined to measure the rate of disappearance of $P^{32}$ from the red blood cells (Fig. 1). The next day the cells were relabeled with $P^{32}$ and the blood volume again determined. Immediately thereafter 500 cubic centimeters of 6 per cent dextran in normal saline were injected intravenously during a period of approximately 1 hour. After completion of the infusion, blood samples were obtained at intervals of ¼, ¾, 1¼, 2½, 3¾, 5, 6¼, 8½, and 22 hours and the radioactivity determined. The radioactivity present as a result of the initial labeling of the cells was calculated and subtracted from the observed values. This was done by extrapolation of the curve for the disappearance of $P^{32}$ from the red blood cells (Fig. 1, line *A* and line *B*). In order to obtain a graphic picture of the effect of dextran upon the blood volume, a third line (Fig. 1, line *C*) was drawn. This line represented the anticipated in vivo rate of disappearance of $P^{32}$ from red blood cells after second labeling; line *D*, the numerator N, for calculation of blood volume at any given time.

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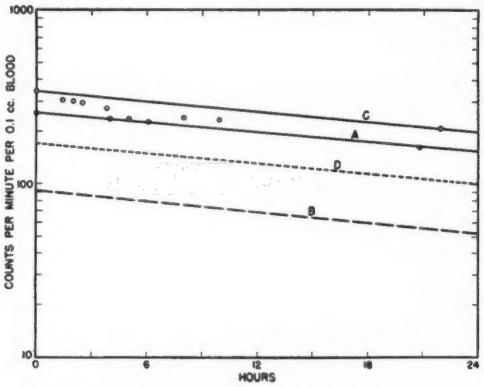


Fig. 1. Left, Graphic presentation of data of patient A.H. Line *A*, in vivo rate of disappearance of $P^{32}$ from the red blood cells; line *B*, extrapolation of line *A* from 48 to 72 hours; line *C*, anticipated in vivo rate of disappearance of $P^{32}$ from red blood cells after second labeling; line *D*, the numerator N, for calculation of blood volume at any given time.

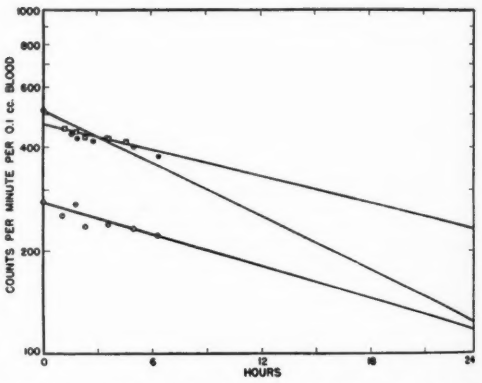


Fig. 2. Right, Line *C* of Figure 1 for the 3 saline controls.

pated rate of disappearance of $P^{32}$ from the red blood cells after the second labeling, provided no change in blood volume occurred (Fig. 2, saline controls). The blood volume at any time was calculated from the equation:

$$\text{Blood volume} = \frac{N}{\text{c.p.m. } P^{32}/\text{c.c. blood}}$$

where N is the number of counts per minute of $P^{32}$ injected. However, since $P^{32}$ was disappearing from the red blood cells, N was constantly decreasing, the rate of this decrease being the same as the rate of disappearance of $P^{32}$ from the red blood cells. Then, a fourth line (Fig. 1, line *D*) may be drawn parallel to line *A* to represent the quantity N at any given time.

Seven men from the orthopedic service hospitalized for fractures and otherwise in good clinical condition (with the exception of patient R. Y., who had cirrhosis of the liver) were given the dextran as outlined. Three additional patients from the same service received 500 cubic centimeters of normal saline under similar conditions and served as controls.

## RESULTS

A typical graph of a case is presented in Figure 1, a graph of the saline controls in Figure 2, and the data of all dextran cases are summarized in Table I.

## DISCUSSION

Figure 1 shows that in patient H. A. the rate of disappearance of $P^{32}$ from the red blood cells during a 24 hour period was constant and the half-time was 31 hours. The average half-time for disappearance of $P^{32}$ from the red blood cells was 21.5 hours with a range of 10 to 34 hours. This is in good agreement with the observations of Nieset and his associates and Wasserman and his associates. Table I also shows the reproducibility of blood volume determinations on successive days. Excluding 1 patient (H. A.) with a hypervolemia of unknown etiology the largest difference in blood volume was 350 cubic centimeters; the average was 183 cubic centimeters.

Figure 2 shows that in the saline controls no significant change in blood volume occurred as a result of the administration of 500 cubic centimeters of normal saline.

TABLE I.—CHANGE IN BLOOD VOLUME IN PATIENTS GIVEN DEXTRAN

| Time before or after administration of dextran | Ht. | B.V. (c.c.) | Increase (c.c.) | Ht. | B.V. (c.c.) | Increase (c.c.) | Ht. | B.V. (c.c.) | Increase (c.c.) | Ht. | B.V. (c.c.) | Increase (c.c.) | Ht. | B.V. (c.c.) | Increase (c.c.) | Ht. | B.V. (c.c.) | Increase (c.c.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H. J. | | | R. Y. | | | W. L. | | | L. T. | | | E. S. | | | H. A. | | | A. C. | | |
| Before 24 hr. | 44.5 | 3540 | | 40.0 | 4040 | | 44.5 | 4250 | | 45.0 | 5190 | | 32.5 | 4980 | | 42.5 | 9490 | | 44 | 4460 | |
| Immediately | 45.0 | 3570 | | 40.0 | 3990 | | 44.5 | 4490 | | 44.5 | 4840 | | 32.0 | 5000 | | 41.0 | 10250 | | 44.5 | 4650 | |
| After 15 min. | 40.0 | 4630 | 1060 | 33.5 | 4370 | 380 | 41.0 | 5210 | 720 | 39.0 | 6290 | 1450 | 29.0 | 6320 | 1320 | 39.0 | 10880 | 630 | 40 | 5470 | 820 |
| 45 min. | 38.0 | 4190 | 620 | 37.0 | 4025 | 35 | 39.5 | 5950 | 1460 | | | | 29.5 | 6320 | 1320 | 37.0 | 10750 | 500 | 40 | 5720 | 1070 |
| 1¼ hr. | 41.0 | 4300 | 730 | 35.5 | 4120 | 130 | 42.0 | 5210 | 720 | 39.0 | 6420 | 1580 | 29.0 | 6200 | 1200 | 38.5 | 11120 | 870 | 42 | 5610 | 960 |
| 2½ hr. | 40.5 | 4180 | 610 | 36.5 | 4000 | 10 | 39.5 | 5530 | 1040 | 41.5 | 5670 | 830 | 30.0 | 6120 | 1120 | 35.5 | 11700 | 1450 | 42 | 5440 | 790 |
| 3¾ hr. | 41.0 | 4020 | 450 | 36.0 | 4270 | 280 | 42.5 | 5790 | 1300 | 41.5 | 5520 | 680 | 30.0 | 6300 | 1300 | 35.5 | 13000 | 2750 | 40 | 5340 | 690 |
| 5 hr. | 40.5 | 4000 | 430 | 37.0 | 4100 | 170 | 41.0 | 5210 | 720 | 43.5 | 5040 | 200 | 30.0 | 7070 | 2070 | 37.5 | 13100 | 2850 | 41 | 5370 | 720 |
| 6¼ hr. | 41.0 | 4010 | 440 | 36.5 | 3930 | −00 | 42.0 | 5180 | 690 | | | | 31.0 | 6360 | 1360 | 38.0 | 11950 | 1700 | 43 | 5460 | 810 |
| 8½ hr. | 42.0 | 3790 | 220 | 37.0 | 3830 | −160 | 41.0 | 5210 | 720 | | | | 31.0 | 6700 | 1700 | 37.0 | 11800 | 1550 | 40 | 6100 | 1450 |
| 22 hr. | | | | | | | 45.5 | 4530 | 40 | 44.5 | 4740 | −100 | 31.0 | 5350 | 350 | 41.0 | 10250 | | 43 | 5360 | 710 |

Table I shows that in individuals—including the 1 person with hypervolemia but excluding the 1 patient with cirrhosis of the liver—the maximum increase in blood varied from 960 to 2,850 cubic centimeters, averaging 1,840 cubic centimeters. In 2 cases (W.L. and A.C.) there was a clear-cut double peak in the elevation of the blood volume; in 3 cases (H. J., E. S., and H. A.) there was a distinct tendency for a second peak, although the volume change was not sufficient to consider this a clear-cut change. The sixth patient (L. T.) was not followed for a sufficient period of time to permit observation of a second peak. The maximal changes in blood volume of individual patients occurred from 15 minutes to 6¼ hours after the administration of dextran. When a double peak was observed, the first rise was noted within 45 minutes after completion of the infusion. The secondary peak occurred between 3¾ and 6¼ hours after completion of the infusion. The maximal increase in blood volume (with the exception of patient R. Y., who had cirrhosis of the liver) averaged 33.4 per cent and varied from 27 to 41.4 per cent. Thus, the degree of response in the patients seems to be a function of the initial blood volume. However, further studies would be necessary, particularly in disease states, to make a definitive statement about the relationship between increase in the blood volume and the initial volume.

At 8½ hours after completion of the infusion the blood volume was increased in 4 of 5 patients from 720 to 1,700 cubic centimeters, averaging 1,370 cubic centimeters. In the fifth case—incidentally the smallest initial blood volume and the smallest change—at this time the blood volume had returned to approximately the initial value. In the 5 patients followed for a period of 22 hours the blood volume averaged 220 cubic centimeters above the initial value.

Blood volume increases calculated from changes in hematocrit did not coincide with those obtained by the methods described. The reasons for this discrepancy are not apparent.

No untoward reactions were noted as a result of the administration of the dextran.

## CONCLUSIONS

1. The administration of 500 cubic centimeters of 6 per cent dextran in normal saline to 6 normal individuals produces an increase in blood volume varying from 960 to 2,850 cubic centimeters, averaging 1,880 cubic centimeters.

2. The maximum increase occurred from ¼ to 6¼ hours after completion of the infusion. Definite secondary increases in blood volume occurred in 2 patients and probably in an additional 3 cases.

3. One patient, with cirrhosis of the liver, showed little change in the blood volume.

4. Three patients showed no significant change in blood volume after administration of 500 cubic centimeters of normal saline.

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# THE ROLE OF RADIATION AND OF SURGERY IN THE MANAGEMENT OF UTERINE CARCINOMA

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THE last word has not been written concerning the treatment of carcinoma of the uterus, whether it be that of the corpus or of the cervix. The problem is in such a fluid state that no one can predict the final role of either radiation or surgery. One can, however, by evaluation of the methods and results during former and recent years and by study of the current experimental measures evolve certain policies as to the present standard management of this disease. This we have done for our own guidance, and we present them for the consideration of others who are interested in this field of endeavor.

## CARCINOMA OF THE CORPUS

First, to consider the lesion that arises in the endometrial cavity, spoken of as carcinoma of the corpus or the fundus, which in the past received less thought than cervical cancer. This lack of consideration was based upon a false impression of the favorable outlook in corpus cancer. Study shows, however, that former management resulted in the survival of less than half the patients. In 1936, Arneson (1) cited a survival rate of only 47.4 per cent in a collected series of 2,000 such patients. Recent reports indicate a considerable improvement, an example of which is seen in Table I that depicts the increment in survival rates at the Radiumhemmet (9) during the past 30 years. The percentage has been increased approximately 20 to reach a level at which the outlook for almost two-thirds of the patients is favorable. While such excellent figures do not appear from all institutions, including ours, Norman Miller in 1946 reported a 5 year figure of 64.5 per cent. At the same time his "planned therapy" for a selected group of 96 patients resulted in 77 per cent survivors.

We now turn to our methods and results from 1931 to 1945, during which time the management of corpus carcinoma was conducted in the following manner. Preference was given to the surgical treatment of those patients who were good operative risks, when the disease was thought to be limited to the uterus. About one-fourth received intracavitary tandem radiation prior to operation, while the remainder were treated by immediate surgery. For the poor surgical risks and for those with disease that had extended beyond the uterus, radiation by intracavitary sources and by subsequent x-ray therapy was preferred.

During this time 211 patients with corpus cancer were in our hands throughout their therapy. Three of these, apparently free of cancer, died from other causes less than 5 years following treatment. Of the remaining 208 patients, 115 (55.3 per cent) are well and seem to be free of cancer for 5 or more years after therapy.

For analysis the 208 patients were placed in two groups according to our clinical estimate of the extent of the disease. Those in whom the growth seemed to be confined to the uterus, technically operable, numbered 163 (79 per cent). The technically inoperable group, with growth extended beyond the uterus numbered 45 (21 per cent). The survival rate was 66 per cent in the former and only 15 per cent in the latter class. The technically operable group was divided into three subgroups according to the size of the uterus—no enlargement, increased but not above the size of a 2½ months' pregnancy, and enlargement beyond that size. The survival rate decreased as the enlargement increased in the order of 82, 62, and 34 per cent. Whether the enlargement results from extensive malignant involvement, myomas, or both, the technical difficulties of treatment are increased tremendously. This is reflected in the very low survival rate that attends the very large uteri. Obviously, future therapy for these problems must include special consideration, which will revolve around the technique of preoperative radiation as

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TABLE I.—CARCINOMA OF THE CORPUS AT THE RADIUMHEMMET, STOCKHOLM, IMPROVEMENT IN RESULTS OF THERAPY

| Years | No. of patients treated | Symptom free after 5 years | |
|---|---|---|---|
| | | No. | Per cent |
| 1914–1928 | 149 | 62 | 41.6 |
| 1929–1933 | 213 | 101 | 47.4 |
| 1934–1938 | 264 | 171 | 64.7 |
| 1939–1943 | 354 | 208 | 59.0 |
| 1944–1945 | 177 | 113 | 63.9 |

either external supervoltage therapy, intracavitary multiple source application, or a combination of the two. The work of Arneson (2), Corscaden, Miller, Scheffey and others has convinced most students of this subject that preoperative radiation should comprise the initial step in the treatment of corpus carcinoma. If intracavitary radiation is used, the simple tandem application may be effective in small uteri; but when the cavity is enlarged or distorted, multiple small sources are required for effective dosage. Among the many methods of meeting this requirement, the modified Crossen technique or the Heyman packing method seems to be the most satisfactory, and we are now using them. The results that we report herein, however, are based upon the older tandem applications; and this may well be one of the causes of our poor survival figures.

In the effort to find other defects in our management we divided the technically operable group into four subgroups, depending on the type of therapy (Table II). While this so reduces the samples that the numbers are too small for statistical significance, the analysis does provide suggestive information. Immediate hysterectomy resulted in the loss of 2 out of every 10 patients. Of the failures following immediate hysterectomy, 4 had very early lesions for whom the outlook appeared to be excellent at the time of operation. Preliminary radium, then hysterectomy, saved 26 out of 28 patients, to produce the best results of any type of therapy. In the group treated by hysterectomy and subsequent radiation the loss amounted to 25 per cent. Radiation alone resulted in the survival of only 40 per cent of the patients to give the poorest results of all. This table supports the belief that the greatest success will follow preliminary radiation and subsequent surgery. Immediate operation, whether followed by radiation or not, seems to be a poor second and radiation alone is a very poor third. Naturally, the question arises, "Why treat any of these technically operable patients by radiation exclusively?" In most instances this choice was dictated by constitutional conditions that discouraged radical surgery. As the risk of pelvic surgery decreases, due to improvements in preoperative, intraoperative, and postoperative care, the group of technically operable but constitutionally inoperable patients should become smaller. Indeed, the great superiority of the combined therapy over that of radiation alone justifies a deliberate effort to lift such patients into the operable group, even though this may entail a moderately increased mortality risk.

This statement does not apply to those patients in whom the lesion has spread beyond the uterus. This group consisted of 45 patients. It is seen in Table III that only 15 per cent survived 5 years. The total survival occurred when the treatment consisted solely of radiation. There were no survivals following operation alone and none following surgery with subsequent irradiation. This emphasizes the futility of the average surgical effort in the treatment of corpus cancer after it has spread beyond the confines of the uterus, even if postoperative radiation is used. Because of the frequent difficulty in detecting this spread upon initial examination, the final decision should be reserved until a full course of radiation has been administered and the reaction has subsided. At this time, careful examination under anesthesia with curettage may enable reclassification with assignment to surgical treatment and the accompanying brighter prognosis.

This study and review of the literature have led us to the following alignment of surgery and irradiation in the treatment of corpus carcinoma. They have complementary roles in that radiation should serve as the preliminary step in all cases. Surgery comprising wide total hysterectomy and bilateral salpingo-oophorectomy should be the second

TABLE II.—CARCINOMA OF THE CORPUS AT THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA (1931 TO 1945), RELATION OF CLINICAL EXTENT AND METHOD OF TREATMENT TO 5 YEAR END RESULTS

| Method of treatment | Cancer confined to uterus | | |
|---|---|---|---|
| | No. of patients | Free of cancer | |
| | | No. | Per cent |
| Hysterectomy | 46 | 37 | 80.4 |
| Radium and hysterectomy | 28 | 26 | 92.9 |
| Hysterectomy and irradiation | 24 | 18 | 75.0 |
| Radiation | 65 | 27 | 40.8 |
| Total | 163 | 108 | 66.3 |

TABLE III.—CARCINOMA OF THE CORPUS AT THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA (1931 TO 1945), RELATION OF CLINICAL EXTENT AND METHOD OF TREATMENT TO 5 YEAR END RESULTS

| Method of treatment | Cancer extended beyond uterus | | |
|---|---|---|---|
| | No. of patients | Free of cancer | |
| | | No. | Per cent |
| Radium and hysterectomy | 1 | 0 | 0.0 |
| Hysterectomy | 4 | 0 | 0.0 |
| Hysterectomy and irradiation | 7 | 0 | 0.0 |
| Radiation | 33 | 7 | 21.2 |
| Total | 45 | 7 | 15.5 |

step, unless operation is contraindicated. The contraindications consist of either extension beyond the uterus or such constitutional impairment that the risk of major surgery will outweigh the proved superiority of postradiation operation. Final decision is reserved until radiation therapy and repeated re-evaluations are conducted, with the hope of elevating the patient to the surgical group. If ultimately operation is judged to be unwise, further radiation by both avenues intracavitary multiple small sources and x-ray is administered. This therapy is instituted immediately following the final decision and carried to the full limit of tolerance, as expressed in terms of tissue units. Thereafter, no more intensive radiation is considered. Experience has taught that anything more than palliative therapy for recurrent growths following previous intensive radiation is ineffective and may even be harmful.

Recent literature refers to the theoretic promise of improved results by radical hysterectomy with extensive regional node dissection. This procedure, because of its surgical magnitude and its unproved worth, should remain in the field of clinical experimentation until its value has been determined by the modern pioneers in pelvic surgery. It should be undertaken only by specially trained pelvic surgeons under ideal environmental conditions.

Ultraradical surgery—and by this we mean pelvic evisceration—may have a place as a measure of desperation in the far advanced cases or in the extensive recurrences. This approach also is in the experimental stage, and such procedures should never be undertaken except in desperate circumstances and under ideal conditions for very major radical pelvic surgery—with full recognition of all of its immediate and late hazards, difficulties, and disappointments.

### CARCINOMA OF THE UTERINE CERVIX

Cancer of the cervix is conceded to be more rapidly fatal than that of the corpus, and the survival figures have been proportionately poor. As in the case of body carcinoma, however, these figures have undergone distinct improvement during the past 15 years. The enhancement in the results of radiotherapy at Radiumhemmet (11) is seen in Table IV that depicts the survival rate in successive periods from 1914 to 1943, with an increase from 22.0 per cent in the first series to 41.5 per cent in the last. This table is a modification of that published by Kottmeier (10) in that 32 patients treated secondarily by surgery are deleted as radiation failures. Not included in this table, but appearing in the latest report from Radiumhemmet (10) are the figures upon 602 patients that were treated in 1944 and 1945, with a 5 year apparent recovery rate of 45.2 per cent. The therapy was conducted largely under the direction of Dr. James Heyman (8), who had this to say in another publication: "The improved re-

TABLE IV.—CARCINOMA OF THE UTERINE CERVIX (STAGES I-IV—LEAGUE) AT THE RADIUMHEMMET, STOCKHOLM,* IMPROVEMENT IN RESULTS OF RADIOTHERAPY

| Years | No. of patients treated | Apparent recoveries after 5 years | |
|---|---|---|---|
| | | No. | Per cent |
| 1914–1929 | 1439 | 316 | 22.0 |
| 1929–1934 | 948 | 245 | 25.8 |
| 1934–1939 | 1224 | 459 | 37.5 |
| 1939–1944 | 1356 | 562 | 41.5 |

*Taken from Kottmeier's report

sults are due to a superior judgment in handling the individual case which, in turn originates from increased experience."

This improvement may be due to variation in the quality of material or to actual increased therapeutic results. In order to determine the relative importance of the two, Table V was prepared from Kottmeier's (11) recent report from Radiumhemmet. The table depicts the results in two series of 5 years each, taken 10 years apart, with an overall increment of 15.7 per cent. Consideration by stages shows an increase in the early cases with a decrease in the late ones, and it also shows the improvement in the apparent cure rate in each stage from I through IV to follow the order of 11, 14, 7, and 5 per cent. Not only is the material better, but the actual therapeutic results are also improved.

By use of the formula that Heyman (6) introduced in the last *Annual Report*, we find the average variation due to change in quality of material to be 1.2 per cent, while the average improvement due to therapy is 9.5 per cent.

TABLE V.—CARCINOMA OF THE UTERINE CERVIX, RESULTS OF RADIOTHERAPY AT THE RADIUMHEMMET

| Stage | 1929–1934 | | | 1939–1944 | | |
|---|---|---|---|---|---|---|
| | No. of patients | Percentage in each stage | Relative apparent cure rate per cent | No. of patients | Percentage in each stage | Relative apparent cure rate per cent |
| I | 96 | 10.1 | 56.3 | 141 | 10.4 | 68.2 |
| II | 324 | 34.2 | 37.0 | 707 | 52.1 | 50.9 |
| III | 354 | 37.3 | 16.4 | 397 | 29.3 | 23.2 |
| IV | 174 | 18.4 | 7.5 | 111 | 8.2 | 12.6 |
| Total | 948 | | 25.8 | 1356 | | 41.5 |

Finally the table was subjected to statistical analysis by use of the chi square formula. This showed a highly significant increase in the overall apparent recovery rate. When the therapeutic results were analyzed by stage, they were found to be highly significant in stage II, significant in stage III, and not significant in stages I and IV—due to the small size of the samples. This evidence convinces us that in the Radiumhemmet modern radiation is producing better results, and we earnestly believe that this record will be duplicated by others who keep pace with the progress of modern radiotherapy.

An example is seen in the achievement of McKelvey who reported a 53.6 per cent survival rate from radiation therapy for 297 patients. In discussing this record McKelvey listed three major factors: more early cases, meticulous care of the patient and of the irradiation details, and hospitalization during the entire treatment at which time unceasing efforts are made to improve the patient constitutionally by means of vitamins, high protein diet, and by multiple transfusions if necessary. This report strengthens our conviction that radiation, with modern medical care, has not reached its ultimate effectiveness in the treatment of cervical carcinoma.

A similar experience has been ours at the Hospital of the University of Pennsylvania. During the period from 1930 to 1945, three successive 5 year series showed the following survival rates: 28.6 per cent, 39 per cent, and 44.8 per cent.

A more detailed analysis of our last 5 year series is seen in Table VI, with the patients grouped as to the clinical stage of advancement by the League of Nations classification. While no patients who did not have invasive carcinoma are included, the high percentage of early lesions is striking. Approximately 1 out of every 4 patients with stage I cervical carcinoma did not respond to therapy, and slightly less than one-half of the stage II cases responded. By combining stages I and II, the survival rate is 57 per cent, while in the more advanced stages (III and IV) 25 per

cent survived, to emphasize the importance of early diagnosis and treatment. This improvement in radiation results (no surgically treated patients are included) may be ascribed not only to more early cases but also to increased therapeutic achievement, due to the following policies: the treatment of the patient as a whole, rather than the simple attack upon her cervical cancer; an alteration in the sequence of radiation with the initial treatment by x-ray and the subsequent treatment by local multiple small sources, the concept of tissue dosage with the effort to reach proper levels by a combination of x-ray and radium therapy, and finally, the closest co-operation between the departments of radiology and gynecology, with the individualization of each problem and frequent consultation between the senior members of both departments.

Thus, it is obvious that radiological therapy for cervical carcinoma is not static nor have the results reached a plateau, as some claim. Close study reveals these pessimistic claims to be based upon figures that include all the data—from the first reports to the present and not upon a breakdown into 5 year groups, as we have done in this study. It is only by analysis of the recent reports that the true picture of the present day results are obtained, and it is only by continued effort to increase the effectiveness and the safety of radiotherapy that future results will exceed those of the present reading. Despite the promise of modern radiation therapy, it must have its limitations. By recognition of these limitations and by the consideration of alternate or supplementary measures, further increase in the survival rates may be expected.

Concerning immediate operation as the alternate measure, one naturally feels the compelling desire to excise a malignant lesion from the body of a patient when such a procedure is feasible. We must not fall prey to this urge in the treatment of cervical cancer, however, unless proof is offered in the future of the long term superiority of the surgical approach over the less dramatic and less glamorous radiological treatment. The radical operation for cervical cancer is one of the most major procedures in gynecology today. Those who are familiar with its technical difficulties and its potentialities of injury, shock, and hemorrhage are unanimous in the conviction that this operation should be undertaken only by one who is particularly trained for the purpose and under environmental conditions that are ideal for its accomplishment. Furthermore, anything less than the radical procedure, consisting of total hysterectomy with excision of the regional lymph nodes, the parametrial, pararectal and paravaginal tissues, and the upper vagina is futile. Meigs (13) and his group have done 280 combined radical hysterectomies and pelvic lymphadenectomies with but 2 deaths, neither of which was surgical. Brunschwig (4) reported the primary surgical mortality of this extended operation upon 225 unselected patients to be less than 0.5 per cent. These splendid accomplishments prove that, under ideal environmental conditions and with consummate surgical skill, the radical operation can be done safely. It is being done, as an experimental project in several large institutions, but it is not ready for general adoption because of its surgical magnitude and because of the lack of proof, that the ultimate results will surpass those obtained by modern radiological therapy. As to surgical results, Meigs reported a 74 per cent 5 year survival rate in 85 instances of invasive cervical cancer (stages I and II League) that were treated by the radical operation. The most recent *Annual Report*, edited by J. Heyman (7), lists 201 operative cases (stages I and II League) collected from 9 different clinics with a 5 year apparent recovery rate of 63.7 per cent. Con-

TABLE VI.—CARCINOMA OF THE UTERINE CERVIX AT THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA (1940 TO 1945), RESULTS OF RADIATION THERAPY

| Clinical stage* | No. of patients | Per cent | Relative apparent recoveries | |
|---|---|---|---|---|
| | | | No. | Per cent |
| I | 46 | 25.0 | 34 | 74.0 |
| II | 68 | 37.2 | 31 | 45.6 |
| III | 55 | 30.1 | 15 | 27.3 |
| IV | 14 | 7.7 | 2 | 14.3 |
| Total | 183 | 100.0 | 82 | 44.8 |

*League of Nations classification

cerning this report Heyman states: "A direct comparison of the cure rates in operative cases and in those treated by radiotherapy only is not justifiable since the operative series relates to highly selected material. A series of cases treated by radiotherapy only and similarly selected is not available." Not only is this true, but comparison of the results of old radiation techniques to the recently reported operative survivals obviously would weigh the evidence in favor of surgery. Both the radical operation and the modern concepts of radiation therapy have been in vogue too little time for evaluation of their ultimate effectiveness. Until sufficient time elapses to permit the accumulation of adequate data for the comparison of the two, the keystone of the day to day therapy for invasive cervical cancer should continue to consist of radiation.

As to the complementary use of radiation and surgery, this field should be explored further, in the form of clinical experimentation, in the care of both the regional lymph nodes and the radioresistant tumor. Regarding lymph node involvement the following points should be considered: the incidence of involvement, the effect of x-ray therapy, the safety of surgical removal and the effectiveness of this procedure. Judging from information furnished by several writers, the incidence of involved pelvic nodes in the "operable" cases seems to range from 18 per cent to 34 per cent. Anent to the effect of x-ray therapy, the postradiation persistence of positive nodes seems to range from 16 per cent to 25 per cent. According to Nathanson the surgical removal of nodes is a reasonably safe procedure if done extraperitoneally by an expert, and it may be done transperitoneally with similar safety, as demonstrated by the Meigs' series. The therapeutic results of node dissection, as judged by available scanty reports, have not been promising. Morton reported a 5 year survival of 6 out of 16 patients with involved nodes that were removed surgically, but 3 died subsequently of recurrence. Meigs stated that 5 of 19 patients with positive nodes that were removed are living and well 5 years after operation. Both authors included patients for whom radical hysterectomy was done also. While the matter of node involvement demands attention, sufficient data have not been accumulated to catalogue its management, as yet. In the past, radiologists have been reluctant to administer adequate dosage to the node bearing areas, because of the danger of injury to vital structures. With improvements in the technique of radiation and with the adoption of tissue unit thinking it may be feasible and safe to administer a cancerocidal dose to the regional lymph nodes. Since their surgical removal by experts is reasonably safe, the logical tentative approach seems to consist of modern adequate radiation therapy to be followed by excision and microscopic study. This experiment would serve the dual purpose of determining the destructive effectiveness of radiation and of judging the value of postirradiation lymphadenectomy. Until the operative technique has been developed fully and until its efficacy has been established, it should remain in the hands of skilled pelvic surgeons who are equipped to conduct it as a clinical experiment.

A second surgical supplement to the radiologic treatment is seen in the radical operation for radioresistant tumors. About 25 per cent of early cervical cancers do not respond to radiation. At present no rule of thumb exists for the determination of radioresistance, and we must depend upon repeated smears, biopsies, and clinical observations. The importance of this problem is stimulating much experimental work. It is hoped that very soon the early recognition of radioresistance will permit appropriate surgical measures prior to advancement beyond the scope of any therapy. Until then we must depend upon the forementioned diagnostic measures.

A further indication for surgery lies in the obvious local recurrence of the disease, following full radiation and in the absence of palpable parametrial extension. It is well recognized that secondary intensive radiation therapy for local recurrences should not be undertaken because of the great likelihood that it will simply add fuel to the malignant flame. Thus, the only recourse is that of wide surgical excision.

The final postradiation surgical approach is mentioned for completeness but not for

general adoption. It consists of the very radical pelvic exenteration in the advanced case that may finish the patient up, if she survives, with a wet colostomy. Brunschwig (3) reported upon 100 such operations with a 26 per cent surgical mortality. Twelve per cent have survived over 35 months. Brunschwig stated that this type of surgery should not be undertaken except by those well qualified in the broadest sense to deal with the major surgical problems of the pelvis and the abdomen. Our experience with this procedure has been limited and unfavorable. Based upon this experience and that of many others, we are loathe to undertake it, unless convincing evidence should be produced in the future that it is justifiable in terms of prolongation of life and in terms of reasonable comfort during that period of prolongation.

## SUMMARY

This study was made in order to crystallize our thinking as to the modern day to day management of uterine carcinoma. In cancer of the corpus the complementary use of radiation and surgery is increasing the survival rate. For the inoperable cases, both low intensity intracavitary packing and x-radiation are indicated.

In cervical cancer, primary radiation by external and local approaches remains the keystone of therapy, while the supplementary use of surgery has certain limited indications.

For both conditions the recent introduction of radical and ultraradical measures is a commendable experimental undertaking that may add much to our therapeutic armamentarium in the future.

For the present, however, it seems to be both wise and humane not to abandon the proved methods in favor of the more dramatic and more hazardous but unproved measures in the day to day treatment of this disease.

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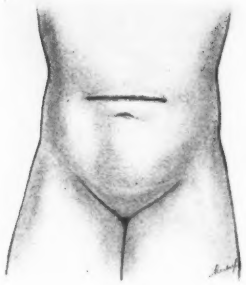

Fig. 1.

Fig. 2.

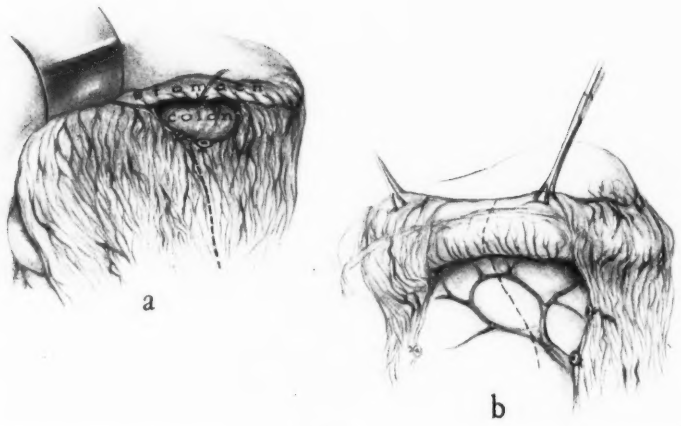


Fig. 3.

Fig. 1. The transverse incision is about 1 inch above umbilicus; ordinarily the right rectus is completely severed, the left only partially.

Fig. 2. Line of complete incision. The upper part is made first. This, when made, interrupts all vascular and lymph channels to and from entire portion to be removed.

Fig. 3. Splitting omentum up to site of colon section and cleaning area of section constitute the first operating step in technique.

*Physiologic Resection of the Right Colon.—J. Peyton Barnes.*

# PHYSIOLOGIC RESECTION OF THE RIGHT COLON

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THE surgical attack on a malignant lesion, wherever located, is ordinarily carried out according to well established and thoroughly accepted principles. One such basic principle is that, whenever possible, the blood supply to and the lymphatic vessels from the lesion be severed before the lesion itself is removed or manipulated. This is to prevent forcing, by such manipulation, malignant cells into the areas beyond the site of surgery via the blood and lymph channels. It is not always possible to achieve the ideal in this respect, but when this principle can be utilized, it most assuredly should be. The various techniques for surgery of cancer of the breast uniformly and invariably endorse and employ this principle, and no one would think of doing otherwise.

Resection of the right colon has become a very standardized procedure, and a search of recent literature plus a visit to some of the country's largest clinics show that the same technique is rather universally employed. After determining the operability of the lesion, the surgeon incises the peritoneal reflection just lateral to the cecum and ascending colon, carrying the incision upward around the hepatic flexure and downward around the cecum onto the posterior layer of the ileal mesentery. Then the whole right colon with the growth is mobilized along with the terminal ileum, and the entire mass carried toward the midline. From here on there are minor variations in technique regarding the ligation of vessels and the type of anastomosis, but the really important feature of the whole procedure is, it seems to me, that the principle of severing the vascular and lymphatic channels of the lesion *first* has been grossly violated. Furthermore, the act of mobilizing the cecum and ascending colon with the growth necessarily demands a great deal of rough handling of the tumor itself, and, if there is anything to the theory that malignant cells can be manu-

Fig. 4. Section of colon is usually done between clamps, as shown, no matter what type of anastomosis is to be done later, in order to keep the field perfectly clean and dry. The space behind the mesocolon is entered, and the mesocolon is separated from all posterior relations just in the incision line, ligating each vessel separately. This dissection is very easy, and any nodes are readily seen.

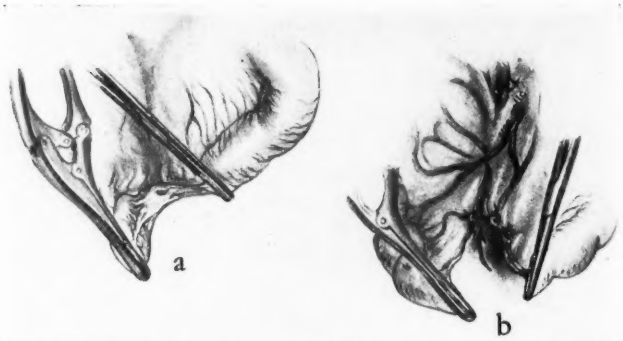


Fig. 5. On reaching the deepest part of the dissection one has usually either cut the ileocolic artery or is very close to it, and the lower section of the incision is now made, cutting ileum between clamps as shown.

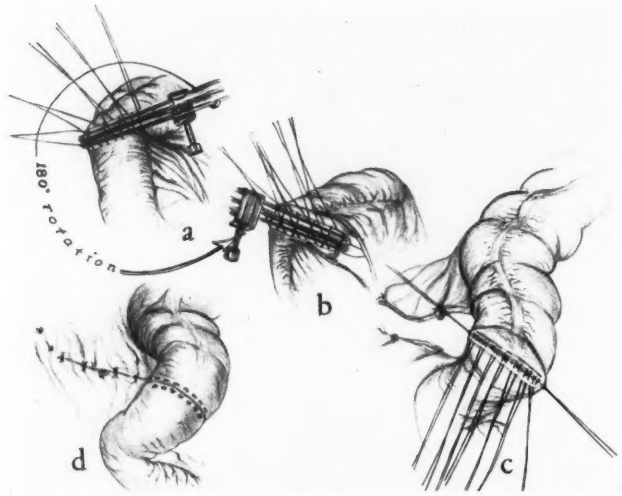


Fig. 6. The clamps are approximated with a small screw clamp (a). A two row anastomosis carried out. The method of placing the sutures as shown results in the smallest possible amount of bowel end being turned in yet gives maximum security.

ally expressed into the lymphatic channels, they most assuredly are by this technique. Finally, after careful consideration of all the anatomical factors involved it seems evident that violation of these two accepted surgical principles is, in the case of the right colon, wholly unnecessary. A technique was then planned so that these principles would be obeyed, not violated. This technique cannot possibly be a new procedure, and the technique now to be described observes these principles far better.

PROCEDURE

1. A transverse incision, cutting both recti about 1 inch above the umbilicus is used (Fig. 1).

2. Resectability is decided upon.

3. The site for section of the colon is established, usually a little to the right of the main trunk of the midcolic artery (Fig. 2).

4. The omentum is now split up to site selected for colon section (Fig. 3a, 3b).

5. The colon is cleared of all fat at the site of section and cut between clamps. A straight

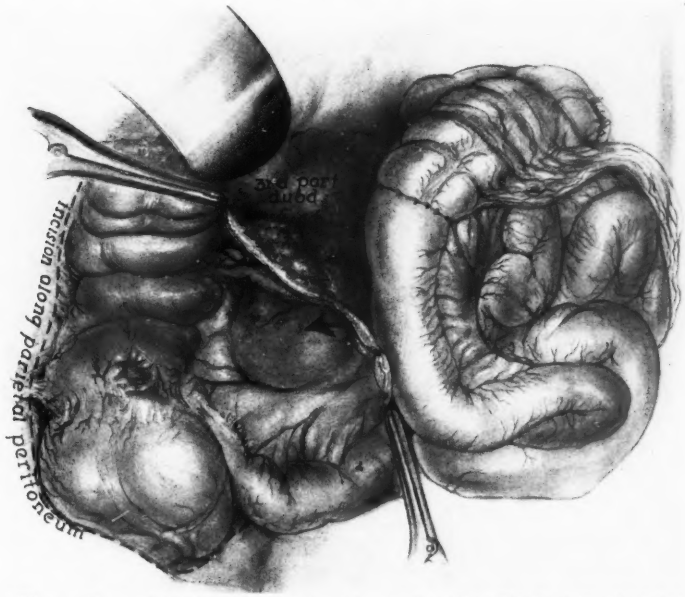


Fig. 7. Removal of the entire specimen is now in order. The first step here is to make the incision through parietal peritoneum lateral to cecum and ascending colon, as indicated by dotted line. After this is made, the dissection shown in this illustration is begun from above downward, and from within outward.

Ochsner clamp is used on the distal end if an end-to-end closed type of anastomosis is contemplated (Fig. 4a).

6. Beginning at this site of colon section, working from above downward, the colon and transverse mesocolon with all vessels and lymph nodes are separated from all posterior relations. As the dissection proceeds downward, all vessels are identified, doubly ligated, and cut (Fig. 4a, 4b). The line of this first incision is indicated in Figure 2, and in completing it one sections a branch of the middle colic, the right colic, and the ileocolic arteries.

7. When this incision as described is complete, the site for section of the ileum is selected and cleared. Since metastases are known to travel along the ileocolic artery, one must be sure to include this. The ileum is then cut between clamps as shown in Figure 5a and b. Note direction of handle of clamp on proximal ileal end. The reason for this is that when the ends of bowel are approximated for anastomosis the clamp on the ileal end will lie alongside that on the distal colon. The mesentery of the ileum is now incised upward, ligating and cutting all vessels separately until this incision joins the first one made from above downward through the transverse mesocolon (Figs. 2 and 5a, b).

8. Without further dissection, the Ochsner clamps on the end of distal colon and proximal ileum segments are brought together, and a two-row, end-to-end closed anastomosis performed (Fig. 6). However, the type of anastomosis, open or closed end-to-end or end-to-side, is a matter of choice and expediency. Poth[1] has described a technique for open anastomosis which is extremely satisfactory and is the writer's choice when a closed type is not feasible.

9. The mesenteric defect is now closed, interrupted sutures being used and placed from the posterior surface. Thus, the blood vessels are more easily avoided, and the anterior or smooth surface of the mesentery remains smooth and free of suture knots (Fig. 7). At

[1]Poth, Edgar J. A technique for suturing bowel. Surg. Gyn. Obst., 1950, 91: 656-659.

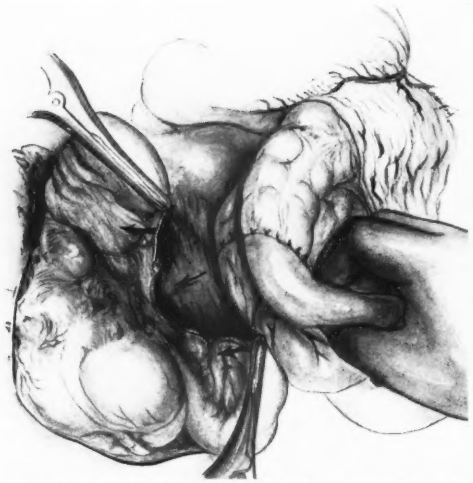

Fig. 8. Continuing the removal of the ascending and transverse colon directly toward the lesion. Identification of the duodenum and ureter is very easy. The field is remarkably dry, and the lesion is removed last of all.

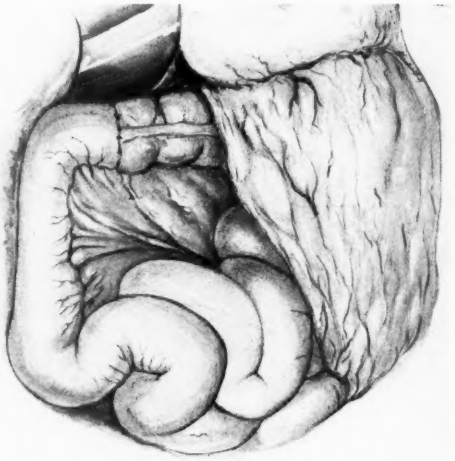

Fig. 9. The completed operation. A few interrupted sutures will serve to anchor the colon and the terminal ileum adequately, and the entire area is pretty well reperitonealized.

this point, except for removal of the lesion plus its attached large and small bowel, the operation is complete. The field has, or should have been, dry and clean throughout. Very little oozing has occurred, and almost no bleeding, and no extensive packing of raw spaces has been necessary. The vascular and lymph channels to and from the lesion have all been severed, and, best of all, the lesion has received an absolute minimum of manipulation.

10. Now one is ready to remove the right colon, lesion, and terminal ileum. At this point we incise the peritoneum lateral to the colon along the dotted line (Figs. 8 and 9) exactly as is done in the present standard technique *as the first step*. By doing so at this point stripping up of peritoneum beyond the desired line is prevented. The colon is not mobilized from without inward.

11. All vascular and lymphatic channels to and from the lesion have now been severed. The anastomosis is complete. Beginning medially and above, working outward and downward, the right colon, mesocolon, with all involved nodes, vessels and ileum are carefully cleaned from the underlying structures. This procedure removes the lesion *last of all* (Figs. 7 and 8). Very noteworthy is the fact that ligating all the vessels first reduces greatly the amount of oozing in the large raw space.

12. The colon and ileum are laid over the raw area (Fig. 9). A few interrupted sutures suffice to fix the colon and ileum adequately, and the abdomen is closed.

## SUMMARY

The technique described adheres to the principle that the blood and lymph channels of a lesion should be severed before manipulating the lesion itself. In this location this technique is very easy to carry out—much easier than the procedure now so widely in use. Furthermore, in a very limited experience with it, I feel sure the patients have much less operative shock.

The advantage of working in a clean, dry field at all times is impressive. As stated previously, the procedure now seems so reasonable and based on such good surgical principles that I cannot believe it to be a new departure, but merely the dusting off of a very old (albeit long-forgotten) technique.

# INTRAMEDULLARY NAILING IN THE PRESENCE OF INFECTION

## An Experimental Study in Dogs

H. LOWRY RUSH, JR., M.D., WILLIAM THOMAS FITTS, JR., M.D., F.A.C.S., JOHN GIBBONS, M.D., and EDWIN W. MONROE, M.D., Philadelphia, Pennsylvania

IN recent years intramedullary nailing has become a recognized procedure for the treatment of several types of fractures. In certain fractures of the femoral shaft it is probably the best method now available. Great dispute has arisen over the safety of using intramedullary nailing in the presence of contamination (as in open fractures) and the advisability of removing the nail if infection develops. It seemed worth while to perform experiments that might test the effect of intramedullary nailing on fracture healing in the presence of gross contamination.

The dog's ulna at the junction of the middle and distal thirds provides an excellent site for the study of fracture healing. A fracture at this level heals without any applied method of immobilization because of the radius, which remains intact and maintains length of the ulna fragments, and the strong interosseous membrane, which gives some stability to the ulna fragments and tends to limit rotation. Experiments[1] on noninfected fractures of the dog's ulna at this level showed that the insertion of an intramedullary wire allowed earlier union than when a wire was not used (Fig. 1). It was believed that the increased stability afforded by the wire was responsible for the more rapid rate of healing. It appeared that this stability outweighed the untoward effects of the wire, namely destruction of the marrow cavity and the presence of a large foreign body. When the nail was divided at the fracture site, eliminating its immobilizing effect, healing took longer on the nailed than on the unnailed side (Fig. 2).

In the study herein reported we have added the factor of gross contamination to the experimental procedure described. We hoped to determine if infection would alter the increased rate of healing afforded by the intramedullary wire.

### EXPERIMENTAL PROCEDURE

Ten mongrel dogs were operated on. Intravenous sodium nembutal (25 mgm./kgm.) was used for anesthesia. Both forelegs of each dog were shaved but the operative procedure was carried out without sterile precautions. A 2 inch incision was made directly over the ulna at the junction of the middle and distal thirds, where the bone is subcutaneous. The ulna was exposed and cleaned of muscle and tendon attachments without stripping the periosteum. A one strand Gigli wire saw was passed around the bone and used to produce a transverse fracture. A Kirschner wire, of a diameter slightly less than the diameter of the medullary canal, was inserted into the proximal end of the medullary cavity and driven retrogradely through the medullary cavity until it protruded from the olecranon. A small incision was then made over the olecranon, and the wire pulled through the proximal fragment until its distal end was even with the fracture site. The fracture was reduced and held in place while the wire was driven across the fracture site and into the medullary cavity of the distal fragment for approximately 1 inch. The part protruding from the olecranon was then cut off level with the bone.

To produce contamination, street dirt and finely divided autogenous muscle (one 4 c.c.

From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia.

Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, San Francisco, November 5 to 9, 1951.

[1] FITTS, W. T., JR., ROBERTS, B., SPOONT, S. I., and RITTER, V. W. The effect of intramedullary nailing on the healing of fractures; an experimental study. Surg. Gyn. Obst., 1949, 89: 609.

a b

Fig. 1. Dog's ulnae fractured bilaterally at similar levels with a Gigli saw. Roentgenograms taken 10 weeks after fracture. Union on pinned side (a). Nonunion on the unpinned side (b).

a b

Fig. 2. Dog's ulnae fractured bilaterally at junction of middle and distal thirds. Wire divided at the fracture site (a). Roentgenograms taken 10 weeks after fracture. Healing is better on the unnailed side (b).

spatula full of each) were introduced into and around the fracture site and adjacent tissues. The wound was closed with interrupted silk skin sutures without drainage. The small incision over the olecranon was closed in a similar manner but this wound was not contaminated.

The opposite ulna was operated upon in an identical manner, the only exception being that no internal fixation was used. The fracture site was contaminated exactly as described for the nailed fracture. The intramedullary nailing was carried out alternately in the right and left forelegs so that 5 dogs had wires in the right ulna and 5 had wires in the left ulna. Four dogs received penicillin in doses of 150,000 units beginning at the day of operation and every other day for 5 doses.

Because of the identical fractures in each dog, the only difference between the two sides being the presence of the Kirschner wire, each dog served as its own control. Thus differences in diet, activity, age, concommitant disease, and nutritional state did not have to be considered when comparing the fracture healing on the two sides.

## RESULTS

*General.* All the wounds became grossly infected and were open and draining purulent material by the fifth postoperative day. Cultures of the wounds of two dogs showed the infecting organisms to be the same bilaterally; viz., on both pinned and unpinned sides of the first dog, Bacillus proteus, Staphylococcus aureus, Bacillus subtilis, Bacillus coli; and on both sides of the second dog, Bacillus coli, hemolytic Staphylococcus aureus, hemolytic Staphylococcus albus, alpha streptococcus, Clostridium welchii. No local treatment was given to the wounds. The dogs receiving penicillin showed less spreading soft tissue infection, fewer palpable axillary lymph nodes, and a milder systemic reaction than those not receiving antibiotics. In 8 of the dogs no significant difference was noted in the time required for cessation of drainage and spontaneous wound closure on the two sides

a b

Fig. 3. Bilateral fracture with contamination. Five weeks after fracture. Union is progressing more rapidly and the infection is less evident on the pinned side (a).

a b

Fig. 4. Same dog as Figure 3. Roentgenograms taken 16 weeks after fracture. Healing on the pinned side (a). Nonunion on the unpinned side (b).

a b

Fig. 5. Bilateral fractures with contamination. Roentgenograms taken 5 weeks after fracture. Note great amount of bone absorption on the unpinned side (b).

a b

Fig. 6. Same dog as shown in Figure 5. Roentgenograms taken 16 weeks after fracture. Union only on pinned side (a).

a b

Fig. 7. Bilateral fracture with contamination. Roentgenograms taken 3 weeks after operation. Note beginning sequestration on unpinned side (b) and abundant periosteal reaction on pinned side (a).

a b

Fig. 8. Same dog as Figure 7. Roentgenograms 9 weeks after operation. Better healing on pinned side (a).

a b

Fig. 9. Bilateral fracture with contamination. Roentgenograms taken 4 weeks after operation. Note the extensive periosteal reaction on the pinned side (a) and bone absorption on unpinned side (b).

a b

Fig. 10. Same dog as Figure 9. Roentgenograms 16 weeks after fracture. More solid union on pinned side (a).

a b

Fig. 11. Bilateral fracture with contamination. Roentgenograms which were taken 3 weeks after fracture. Note sequestration which has occurred on the pinned side (a).

a b

Fig. 12. Same dog as in Figure 11. Roentgenograms taken 16 weeks after fracture. Note more solid union on unpinned side (b). This case is an exception to the general trend of earlier union on the pinned side.

the mean time for closure being 3 weeks. In the remaining 2 dogs, however, it was noted that the wounds on the unpinned side remained open and drained considerably longer than the wounds on the pinned side. In the latter 2 dogs, closure was complete within 4 weeks on the pinned side and 7 weeks on the unpinned side.

All 10 dogs walked by the third postoperative day and did not favor either leg throughout the period of observation, which, for the 6 dogs which survived, is now 9 months for the shortest period and 11 for the longest period of time.

Four deaths occurred during this period of observation. The cause of death was determined in each instance by postmortem examination. One dog died of septicemia 2 weeks after operation; this dog did not receive penicillin. Three deaths were the result of distemper and occurred at 4, 6, and 10 weeks respectively after operation. Two of the latter dogs received penicillin postoperatively. Postmortem examination of these 4 dogs showed more abundant callus formation and less bone absorption on the pinned side than on the unpinned side. One dog (No. 9) showed weak clinical union of the pinned ulna and nonunion of the unpinned ulna. The other 3 dogs showed no union of the ulna on either side. Multiple microscopic sections through the ulna at distances from the fracture site showed that no infection had spread up the medullary cavity on either the pinned or unpinned sides.

*Roentgenological.* The 4 dogs that died did not have roentgenographic evidence of bony union on either side at the time of death, although 1 had weak clinical union on the pinned side. In these 4 dogs, however, as well as in 4 of the 6 surviving dogs, successive roentgenograms showed a definite trend toward earlier and more abundant callus formation on the pinned side and toward earlier bony union of the fractures on the pinned side (Fig. 3 to 10).

Two of the 10 dogs were exceptions to the general trend toward better healing on the pinned side (Figs. 11 and 12).

A common finding on the pinned side was that of extensive periosteal callus at a distance from the fracture site; we believe that this must have been due, in part at least, to mechanical stress factors contributed by the intramedullary pin. There was no evidence that the infection had spread up the medullary cavity of the ulna on the pinned side.

## DISCUSSION

In general, infection did not prevent the increased rate of healing of the fracture immobilized by an intramedullary nail. The earlier callus formation, the earlier bony union, and the less severe infection on the pinned side in 8 out of the 10 instances were evidences of this fact.

The intramedullary nail, although a foreign body, produced no spread of infection along the medullary cavity as proved by microscopic sections and roentgenograms of the fractured ulna. The infection was limited to the area of the fracture site and to the adjacent tissues.

There is no doubt but that immobilization is better on the pinned side; yet the unpinned side has sufficient stability so that healing occurs under ordinary circumstances although less rapidly than on the more stable pinned side. These conditions may be analogous to the problem in humans when intramedullary nailing gives more rigid fixation than plaster casts or skeletal traction. Although it would be dangerous to carry over any conclusions from these experiments on animals to humans, we believe the experiments do demonstrate the importance of rigid immobilization of fractures in the presence of infection and that rigid immobilization speeds their healing and aids in overcoming the infection.

## SUMMARY AND CONCLUSIONS

1. Identical fractures of the dog's ulna were produced bilaterally and were grossly contaminated. On one side a Kirschner wire was inserted through the medullary cavity for rigid fixation; on the opposite side no wire was inserted. Ten dogs were operated on and were followed clinically and roentgenologically.

2. In 8 of the 10 dogs studied, healing was more rapid and infection was less severe on the pinned side. In no instance did the presence of the nail cause spread of the infection up the medullary canal.

3. Even in the presence of contamination the added degree of fixation afforded by the intramedullary nail outweighed its presence as a foreign body and its injury to the medullary cavity.

# CYTOLOGIC PATTERNS IN BENIGN AND MALIGNANT GASTRIC AND ESOPHAGEAL LESIONS

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THE introduction of the abrasive gastric balloon procedure[1] has created an advance in gastric cytology by affording an increased number of better preserved gastric cells. The abrasive balloon has been employed in over 100 different patients suffering with undiagnosed gastric disorders. The first 45 cases that were studied completely by surgical resection offer the material for this correlation between the cytologic smear components and the pathologic lesion entity. The purpose of this presentation is to describe some of the cytologic patterns encountered as compared with the pathologic findings in the various cases examined.

The 45 cases studied are surveyed in Table 1. They include 4 patients without a grossly demonstrable esophageal or gastric lesion, 2 patients with chronic hypertrophic gastritis, 2 patients with chronic atrophic gastritis, 12 patients with benign gastric ulcers, 2 patients with squamous cell carcinoma of the esophagus, 20 patients with gastric adenocarcinoma, and 3 patients with gastric sarcoma. This selection of disease categories demonstrates some cytologic differences observed.

The study of gastric smears should not be limited to the finding of malignant gastric cells alone. The composite picture of all smear elements adds to the understanding of the condition of the gastric mucosa. Attention is focused on the (1) gastric elements, (2) oropharyngeal and esophageal elements, (3) blood elements, (4) nasorespiratory elements, (5) bacterial and parasitic elements, (6) foreign elements, and (7) unidentifiable elements. While the final impression of the gastric smear is derived from all seven sources, in many instances the esophageal and gastric surface epithelial cells may more directly reflect the condition of the mucosa. For this reason a selected variety of pathologic sections is shown accompanied by representative esophageal and gastric epithelial cells found in corresponding gastric smears. In order to establish some degree of uniformity all pathologic sections and cytologic smears were prepared and stained by the Papanicolaou technique and all photomicrographs were taken at 670 magnification (reduced to ×475 in reproduction).

Smear types may be classified into three different categories: (1) the nonmalignant gastric smear containing cellular components devoid of atypical or malignant characteristics; (2) the nonmalignant atypical gastric smear containing atypical cellular components devoid of malignant characteristics; (3) the malignant gastric smear containing pathognomonic malignant cellular components.

## THE NONMALIGNANT GASTRIC SMEAR

Nonmalignant cells include the normal exfoliated cells along with the modifications caused by their exposure to the gastric environment, the collecting, processing, and staining procedures. The gastric smear may contain such general components as are outlined in Table II.

A histologic section of esophagus from a patient without esophageal disease is shown

TABLE 1.—DISEASE CATEGORIES STUDIED

| | No. of cases |
|---|---|
| No grossly demonstrable disease of the esophagus or stomach | 4 |
| Chronic hypertrophic gastritis | 2 |
| Chronic atrophic gastritis | 2 |
| Benign gastric ulcers | 12 |
| Squamous cell carcinoma of the esophagus | 2 |
| Gastric adenocarcinoma | 20 |
| Gastric sarcoma | 3 |
| Total cases | 45 |

From the Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland. Material is utilized from the Cytologic Division of the Department of Anatomy, Cornell University Medical College, the Department of Surgery, New York Hospital, and the Department of Surgery, Memorial Hospital, New York. This work has been partially supported by the United States Public Health Service and the Commonwealth Fund.

[1] PANICO, F.G., PAPANICOLAOU, G.N., COOPER, W.A. Abrasive balloon for exfoliation of gastric cancer cells. J. Am. M. Ass., 1950, 143: 1308–1311.

with accompanying nonmalignant squamous surface epithelial cells (Fig. 1) found in gastric smear. The squamous epithelial cells may be roughly compared to the cervical and vaginal squamous epithelial cells. The superficial cell types which are found in great numbers are large eosinophilic or basophilic cells with a rather voluminous cytoplasmic mass contained within a well outlined irregular cytoplasmic membrane. The regular round or oval nucleus with its fine delicate chromatin network is usually incorporated centrally within the cytoplasm. The cellular clusters show distinct cytoplasmic outlines without evidence of nuclear crowding. The occasional parabasal cell type found especially in the oropharynx have larger nuclei in relation to the size of the cells with the tendency for vacuolization of the cytoplasm. Generally, the squamous cells show excellent preservation.

A histologic section of stomach from a patient without gastric disease is shown with accompanying nonmalignant mucosal surface epithelial cells (Fig. 2) found in gastric smear. The gastric epithelial cells may be roughly compared to the uterine endometrial cells. The surface epithelial cell types are small cuboidal or columnar basophilic cells with a little cytoplasm contained within a poorly delineated cytoplasmic membrane. The small well outlined round or oval nucleus has a fine chromatin network. Cellular clusters show a uniform regularity of the individual cells without evidence of nuclear crowding. Many free or stripped naked nuclear remnants devoid of their cytoplasmic structure are found because of the rapid plasmolysis attributable to the gastric mucosal cell. The mucous secretory cell type may be seen occasionally with unipolar vacuolization sometimes associated with a slight constricting nuclear indentation. No significance is attached to the amount of mucus seen in smears because of its variable occurrence.

### THE ATYPICAL NONMALIGNANT GASTRIC SMEAR

Atypical alterations of the nonmalignant cells result from changes occurring in the nucleus and cytoplasm because of degeneration or inflammation. These changes appear

TABLE II.—GENERAL COMPONENTS OF A GASTRIC SMEAR

*Gastric elements*—derived from the secretions and the exfoliation of gastric cells collecting within the gastric lumen
- Gastric mucosal cells: (1) surface epithelial type, rarely found in well preserved cell clusters; (2) free or stripped naked nuclear remnants, often very numerous because of the plasmolysis resulting from the action of the gastric proteolytic ferments; (3) mucous secretory or signet ring cell type, rare because of the disintegration of the mucus containing vacuole
- Mucus, variable amounts

*Oropharyngeal and esophageal elements*—derived from the exfoliating squamous cells of the oropharynx and esophagus reaching the stomach by the mechanism of swallowing
- Squamous mucosal cells: (1) superficial type, frequently found in well preserved clusters; (2) parabasal type, rare
- Squamous cell nests or pearls, rare

*Blood elements*—derived from the cells of the vascular system by the mechanism of leucopedesis and hemorrhage
- Polymorphonuclear leucocytes, variable number depending on such factors as acute and chronic inflammation and the foreign body response
- Lymphocytic leucocytes, variable number depending on such factors as chronic inflammatory or lymphomatous reactions
- Monocytes, variable number occasionally seen in certain inflammatory conditions
- Macrophages or histiocytes, variable number more frequently seen in certain inflammatory conditions
- Erythrocytes, absent except in active hemorrhage
- Plasma cells, variable number more frequent in chronic inflammatory conditions

*Nasorespiratory elements*—derived from the secretions and the exfoliation of nasorespiratory cells reaching the stomach by the swallowing of postnasal and coughed bronchial discharge
- Mucoid columnar or cuboidal cells of nasal or bronchial origin with occasional goblet cells of bronchial origin
- Ciliated cells of nasal or bronchial origin
- Pulmonary or bronchial histiocytes with pigment ("dust cells") or without pigment

*Bacterial and parasitic elements*—derived from the oropharnyx, esophagus, stomach, nasorespiratory tract and contaminants accumulating before fixation
- Bacteria, various types chiefly cocci more numerous in specimens not fixed immediately
- Fungi, various types chiefly monilia in the form of spores or mycelia more numerous in specimens not fixed immediately
- Parasites, occasional Giardia lamblia

*Foreign elements*—derived from ingested nutrient or inert material. Undigested food cells, variable occurrence

*Unidentifiable elements*—remaining elements difficult for accurate interpretation
- Degenerated or necrotic cells
- Retention debris
- Crystals
- Interstitial cells
- Fibrotic cells
- Duodenal cells, present by duodenal reflux but their identity is not certain

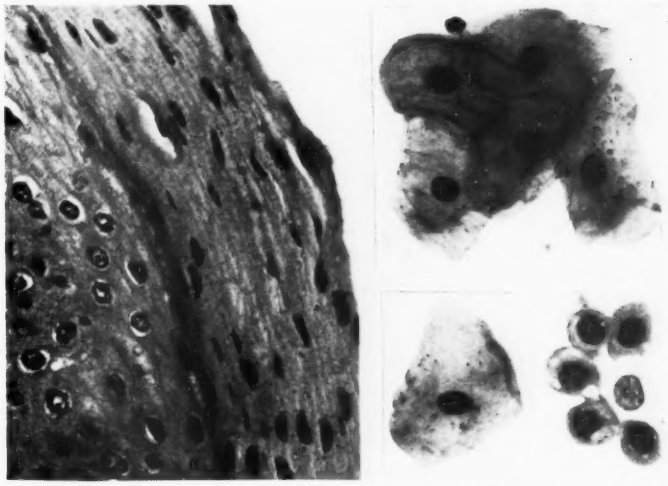

Fig. 1. Histologic section of esophagus and corresponding nonmalignant squamous surface epithelial cells derived from a patient without esophageal disease. ×475.

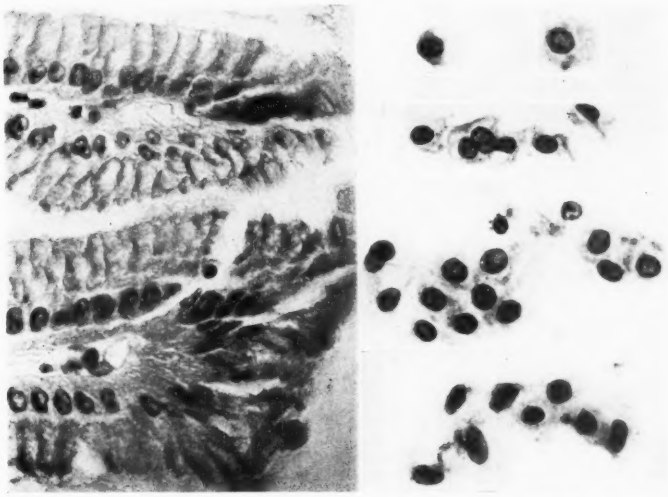

Fig. 2. Histologic section of stomach and corresponding nonmalignant gastric mucosal surface epithelial cells derived from a patient without gastric disease. ×475.

to affect the gastric mucosal cell more than the esophageal squamous cell. The degenerative changes may occur with cellular aging, biochemical digestion, nutritional deficiency, and unphysiologic conditions influenced by such factors as hyperacidity, retention, hormonal imbalance, vitamin deficiency, and anemia. The nucleus may be slightly enlarged and hyperchromatic. There may be pyknosis, karyorrhexis, or karyolysis. The cytoplasm may contain vacuolar inclusions and the cytoplasmic membrane may be distorted,

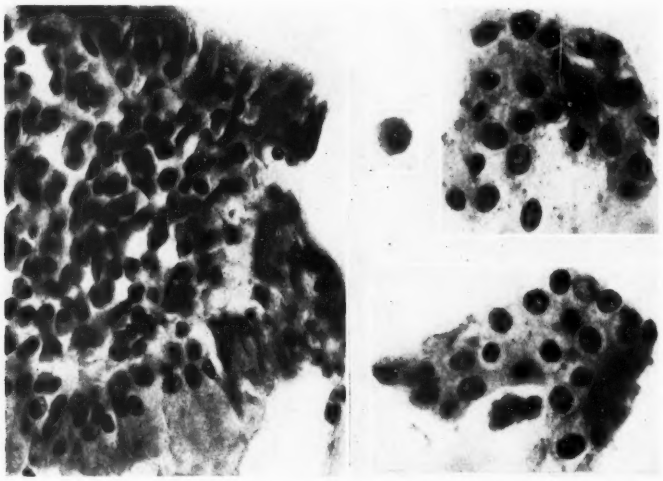

Fig. 3. Pathologic section and corresponding atypical gastric mucosal surface epithelial cells derived from a patient with chronic hypertrophic gastritis. ×475.

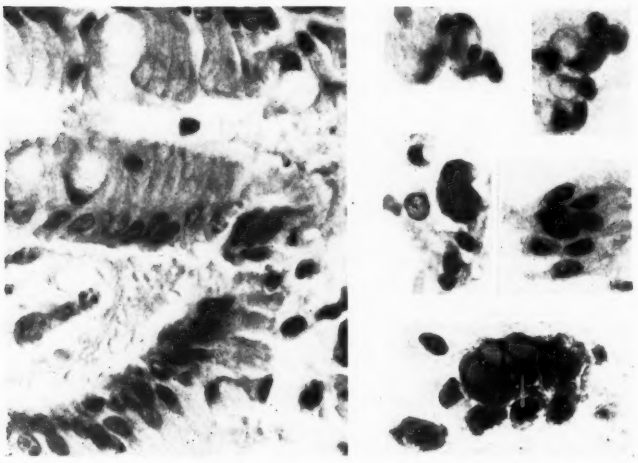

Fig. 4. Pathologic section and corresponding atypical gastric mucosal surface epithelial cells derived from a patient with chronic atrophic gastritis. ×475.

fragmented, or disintegrated. The cellular clusters may show slight anisocytosis and anisonucleosis with some coalescence of the cytoplasmic boundaries. Debris may oftentimes be significant of the degeneration seen in gastric smear.

The inflammatory changes may occur with leucocytic infiltration, cellular necrosis, and ulcerative erosion influenced by such factors as gastritis, ulceration, phagocytosis, and fibrosis. The nucleus may be slightly enlarged and hyperchromatic with a prominent nuclear membrane. The nucleolus and accessory chromatin material may be more prominent. The cytoplasm may contain leucocytic inclusions. The cellular clusters may present slight anisocytosis and anisonucleosis. Polymorphonuclear and lymphocytic leucocytes may be pres-

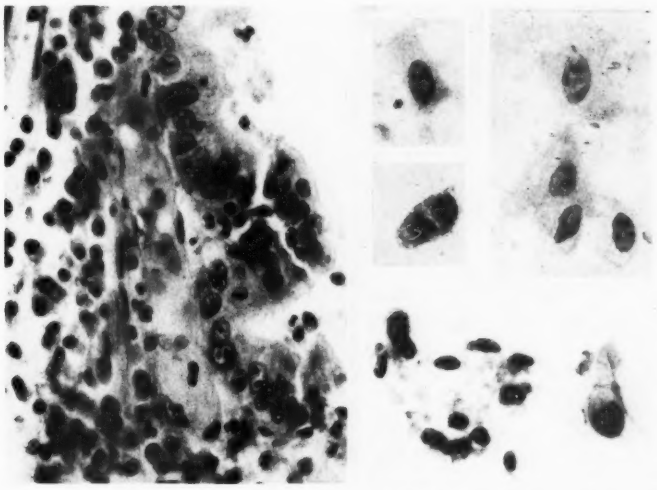

Fig. 5. Pathologic section and corresponding a typical gastric mucosal surface epithelial cells derived from a patient with benign chronic gastric ulceration. ×475.

ent in varying numbers as part of the inflammatory reaction seen in the gastric smear. The reparative processes associated with healing gastric ulcers or postoperative stomachs may often yield atypical and bizarre cells which show changes easily misinterpreted as suggestive of malignancy. In such reparative processes, the active histiocytes performing their phagocytic function complicate the cytologic picture by affording cells quite difficult for evaluation.

A pathologic section from a patient with chronic hypertrophic gastritis is shown with accompanying atypical gastric epithelial cells (Fig. 3) found in gastric smear. In section the gastric mucosa shows hypertrophic changes. The secretory activity of the surface mucosal cells causes only occasional constricting nuclear indentation. Many lymphocytes and plasma cells are found in the interstitium and some lymphocytes are seen migrating through the surface epithelial cells of the mucosa. In the corresponding smears there is an increased amount of mucus with many lymphocytes and gastric cell clusters. The clusters of mucosal cells are interspersed with extracellular infiltrating lymphocytes. The individual gastric cells correspond to the normal superficial cells of the gastric mucosa retaining fair cytoplasmic boundaries with the nuclear structures appearing regular in definition. There is minimal enlargement or hyperchromasia of the nuclei. Vacuolated mucosal cells are rarely encountered in smear. The extracellular lymphocytic cells scattered through the epithelial cells offer an important differentiation from the cluster of normal mucosal cells.

A pathologic section from a patient with chronic atrophic gastritis is shown with accompanying atypical gastric epithelial cells (Fig. 4) found in gastric smear. In section the gastric mucosa shows atrophic changes. A few of the surface cells show their nuclei to be compressed by cytoplasmic vacuolization. There are some lymphocytes and plasma cells found in the interstitium. In the corresponding smears there are a moderate number of polymorphonuclear leucocytes, occasional lymphocytes, and a few atypical gastric cells. Extracellular lymphocytes are encountered rarely. While some of the nuclei of the mucosal cells are little affected by the cytoplasmic vacuolar inclusions, a few nuclei are pressed to one side resulting in the crescent-shaped and hyperchromatic nuclei of signet-ring cells. The signet-ring cell appears prominent especially in view of the scarcity of other epithelial cells.

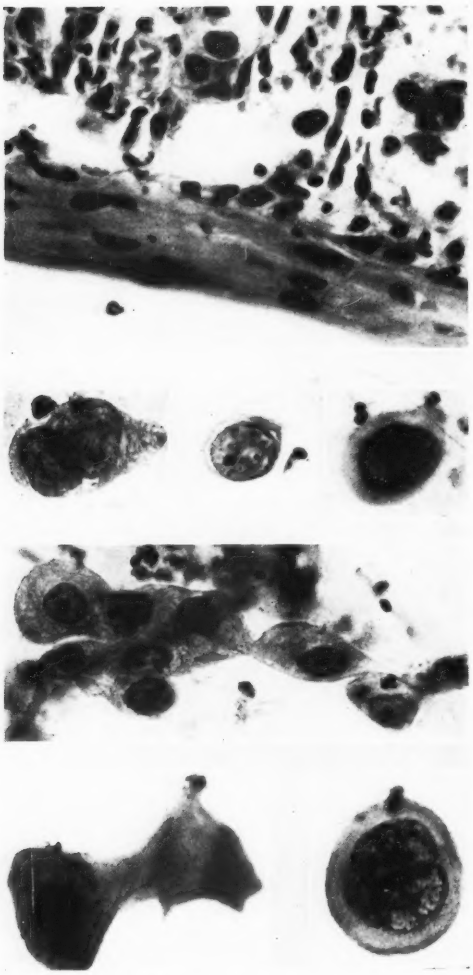

Fig. 6. Pathologic section and corresponding malignant esophageal squamous surface epithelial cells derived from a patient with esophageal squamous cell carcinoma. ×475.

A pathologic section from a patient with a benign chronic gastric ulcer is shown with accompanying atypical gastric epithelial cells (Fig. 5) found in gastric smear. In section there are atypical epithelial cells bordering the ulceration and its granulomatous base. An inflammatory reaction is seen deep to the atypical mucosal cells. In the corresponding smears there are a variable number of polymorphonuclear and lymphocytic leucocytes and a few atypical mucosal cells. The atypical cells display nuclear enlargement with an accentuation of the chromatin material and nucleolar bodies. Nuclear hyperchromasia is rather minimal. Interstitial and fibrotic cells are difficult to identify. The unusual degree of dyskaryosis of the epithelial cells offers speculative value.

The nature of the various atypical changes found in the gastric epithelial cells is not yet clearly understood. The smear findings in many cases overlap. While there is no definite relationship established between atypical and malignant transgressions, certain of the alterations observed in some of the atypical gastric epithelial cells suggest the beginning criteria of malignancy.

### THE MALIGNANT GASTRIC SMEAR

All of the cells seen in a malignant gastric smear are not necessarily malignant. Nonmalignant and atypical cells may also be present. Because malignant cells may be more readily exfoliated by the abrasive balloon, an increased number of abnormal cell clusters becomes significant. The malignant cells may exhibit enlarged, hyperchromatic nuclei with prominent nucleoli and accessory chromatin material. There may be a degree of nuclear or cytoplasmic distortion resulting in "tadpoling." Other bizarre cellular forms may result from cytoplasmic vacuolization, leucocytic or pyknotic cellular inclusions, multinucleation, cellular ballooning, or orangeophilia. Cellular clusters may show crowding with loss of polarity, anisocytosis, anisonucleosis, and loss of cytoplasmic boundaries. Adenocarcinoma can be recognized by these criteria associated with the surface epithelial cell. When the adenocarcinoma cells clearly present these criteria, they allow for a rather high degree of diagnostic accuracy.

Alterations of the gastric mucosa due to the malignant process may be reflected by the prevalence of certain gastric components not ordinarily found in an average nonmalignant gastric smear. Polymorphonuclear and lymphocytic leucocytes may be coincident with acute and chronic gastritis, the signet-ring cell with chronic atrophic gastritis, abnormal

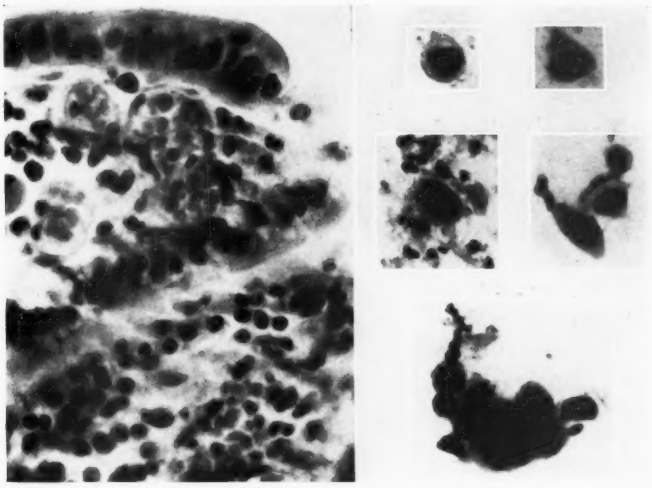

Fig. 7. Pathologic section and corresponding malignant gastric mucosal surface epithelial cells derived from a patient with early superficial gastric adenocarcinoma. ×475.

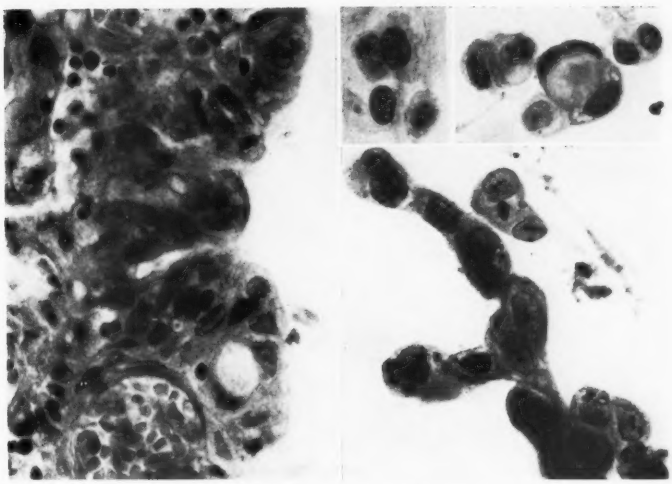

Fig. 8. Pathologic section and corresponding malignant gastric mucosal surface epithelial cells derived from a patient with polypoid gastric adenocarcinoma. ×475.

lymphocytes with lymphosarcoma, histiocytes or macrophages with the phagocytosis of leucocytes and degenerating malignant cells, plasma cells with obscure chronic inflammations, erythrocytes with ulcerative bleeding, undigested food cells with gastric retention, and bizarre cells with eroding deep seated lesions. Some ulcerating intramural lesions may not produce any recognizable malignant cells. In such instances environmental changes may affect the structural characteristics of adjacent surface epithelial cells enough to cause atypical cellular transformations. In these many ways the malignancy may be detected

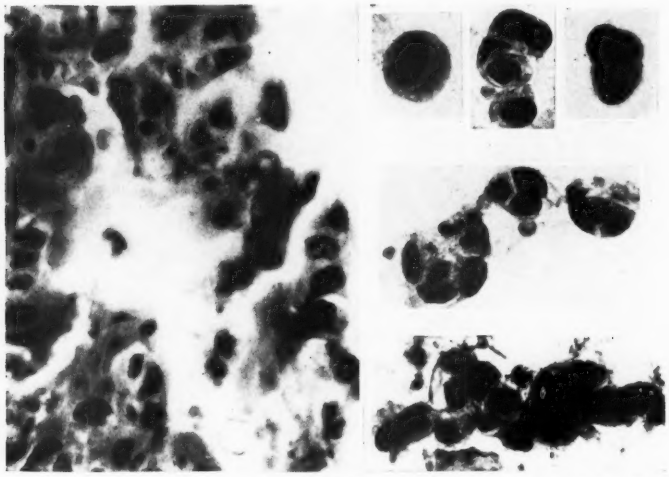

Fig. 9. Pathologic section and corresponding malignant gastric mucosal surface epithelial cells derived from a patient with ulcerating gastric adenocarcinoma. ×475.

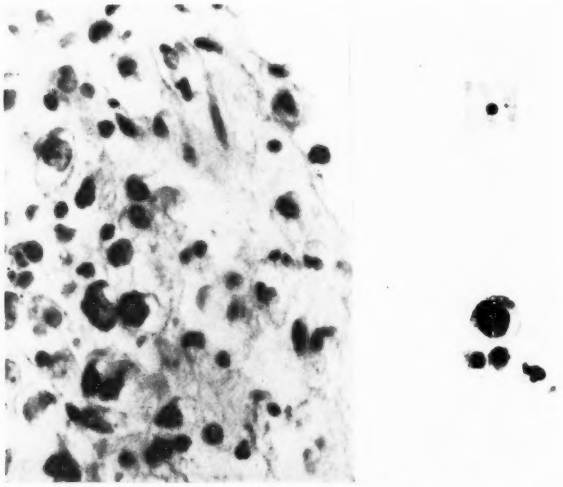

Fig. 10. Pathologic section and rare corresponding malignant cell derived from a patient with reticulum cell sarcoma. An erythrocyte is shown for size comparison. ×475.

indirectly by the gastric smear picture. The abrasive balloon, by affording a better representation of well preserved gastric smear components, is proving to be a valuable instrument in the diagnosis of questionable lesions of the stomach and esophagus.

A pathologic section from a patient with esophageal squamous cell carcinoma is shown with accompanying malignant squamous epithelial cells (Fig. 6) found in gastric smear. In section the lesion shows malignant changes of the surface cells extending well into the esophageal muscularis. Orangeophilic stained cells are seen along the surface of the lesion. Cellular bizarreness and nuclear hyperchromasia increase with the depth of the lesion.

Fig. 11. Pathologic section from adjacent mucosal tissue in the same patient with gastric reticulum cell sarcoma (Fig. 10) and the corresponding atypical gastric mucosal surface epithelial cells derived from the patient with reticulum cell sarcoma. ×475.

The individual cells vary greatly as to their cytoplasmic volume and nuclear size. The stroma shows some lymphocytic infiltration. In the corresponding smears there are many polymorphonuclear leucocytes, lymphocytes, and single malignant cells. The individual malignant cells show an abnormally enlarged round or oval nucleus with a large prominent nucleolus and accessory chromatin material. There is little hyperchromasia of the cells. Some cells are distorted because of cytoplasmic stringing. There are many orangeophilic cells, bizarre cells with malignant cell inclusions, and binucleated cells. The malignant cell clusters show some anisocytosis and anisonucleosis. The large size of the orangeophilic cells and bizarre malignant cells offer little confusion with respect to their squamous origin.

A pathologic section from a patient with early superficial gastric adenocarcinoma is shown accompanied by malignant gastric epithelial cells (Fig. 7) found in gastric smear. In section the malignant changes are restricted to the surface mucosa and submucosa without any apparent muscular penetration. The nuclei of the epithelial cells show hyperchromasia with crowding and anisonucleosis. In the corresponding smears there are many lymphocytes, polymorphonuclear leucocytes, and many single malignant cells. The malignant cells have enlarged hyperchromatic nuclei. The hyperchromasia may often conceal the nuclear detail. The malignant cell clusters show crowding of the irregularly shaped hyperchromatic nuclei. The single malignant cells with their enlarged hyperchromatic nuclei and lack of cellular bizarreness are pathognomonic in their conformity to the criteria of malignancy, suggesting that lesions do not have to be far advanced to be diagnosed cytologically.

A pathologic section from a patient with polypoid gastric adenocarcinoma is shown with accompanying malignant gastric epithelial cells (Fig. 8) found in gastric smear. In section there is a polypoid growth with increased vascularity. There are numerous polymorphonuclear leucocytes infiltrating the stroma. Occasionally the leucocytes are intracellular. In the corresponding smears there are many polymorphonuclear leucocytes and malignant cell clusters. The malignant cells do not present the extent of hyperchromasia and degeneration shown in the other cases of adenocarcinoma. The cytoplasm and nuclear membranes are well defined. The enlarged

nuclei contain prominent nucleoli. Occasional bizarre cell forms are seen containing intracellular leucocytic inclusions. The cytoplasmic inclusions and the sharp definition of the cells are interesting features of this exfoliative lesion.

A pathologic section from a patient with ulcerating gastric adenocarcinoma is shown with accompanying malignant gastric epithelial cells (Fig. 9) found in gastric smear. In section there is an ulcerative erosion that allows for the exfoliation of superficial necrotic and deeper bizarre malignant cells. In the corresponding smears there are many polymorphonuclear leucocytes, lymphocytes, and malignant single cells and cell clusters. Some of the malignant cells show considerable bizarreness containing hyperchromatic cellular inclusions and necrotic remnants within the cytoplasm. The cellular inclusions suggest a phagocytosing reaction to the necrotic lesion.

A pathologic section from a patient with gastric reticulum cell sarcoma is shown with an accompanying malignant cell and erythrocyte (Fig. 10) found in gastric smear. In this section there is an intramural reticulum cell growth eroding through the mucosa into the gastric lumen. The reticulum cells are numerous and well defined with irregular enlarged hyperchromatic nuclei containing prominent nucleoli and accessory chromatin material. There is an increasing amount of cellular bizarreness seen in the deeper portions of the tumor. In the corresponding gastric smears a rare reticulum sarcoma cell is identified. However, there are many other atypical gastric epithelial cells encountered. A pathologic section from the gastric mucosa adjacent to the same eroding reticulum cell sarcoma is shown with the atypical gastric epithelial cells (Fig. 11) found in gastric smear. In section the adjacent mucosa shows atypical epithelial cell changes. The surface cells have enlarged elongated nuclei and show slight hyperchromasia and crowding. The intramural growth is present deep to this atypical mucosal layer. In the corresponding smears already mentioned there are many polymorphonuclear leucocytes, lymphocytes, and atypical cell clusters. The single atypical cells have irregular cytoplasmic borders with enlarged elongated hyperchromatic nuclei. The clusters of cells show a coalescence of the cytoplasm with a loss of cellular boundaries. Appearing to resemble giant cells, these multinucleated structures with enlarged elongated hyperchromatic nuclei are an important finding in this case. The cytology of the atypical surface epithelial cells found adjacent to an ulcerating intramural reticulum cell sarcoma reflects an abnormality of the gastric mucosa. In this way the gastric surface epithelial cell tends to offer an indirect indication of gastric malignancy.

Cells obtained from the stomach and esophagus by the abrasive balloon may contain cytologic information suggestive of an underlying pathologic condition. Not enough is yet known about gastric cytology to diagnose the exact type of benign or malignant lesion on the basis of the smear findings. However, the epithelial cell may potentially reflect certain pathologic conditions involving the esophageal and gastric mucosa. An understanding of the surface epithelial cells and their environmental elements will unfold with the study of collected cases. In this way the gastric smear may become increasingly helpful in the early evaluation of gastric disease. Additional cases are presently being compiled in an expanding test series to estimate the accuracy and feasibility of the abrasive balloon method as a routine adjunct to gastric cancer detection. Results are rather gratifying and justify the expectations already reported.

# THE EFFECTS OF KNOWN COMPRESSION FORCES ON FRACTURE HEALING

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THIS work was projected in an effort to learn how the healing of a fracture is influenced by varying the amount of compression to which the fracture is subjected.

Knowledge of the effects of mechanical forces on bone repair and bone formation gives the surgeon additional insight in the treatment of bone injuries. This field was widely explored in the latter half of the nineteenth century and the relationship of compression and tension forces to the site, number, and orientation of bone trabeculae was noted and finally expressed as Wolff's law. This concept has been challenged in certain of its details but a general relationship between pressure stresses and the outer form and inner trabecular pattern of bone is at the present time widely accepted.

More recently investigations have been conducted to demonstrate the healing response of fractured surfaces following the application of mechanical forces. Distraction of a fracture is thought to predispose to delayed union and nonunion while compression is thought to accelerate healing. Charnley, using a method for obtaining knee fusion by compressing the bone surfaces, described earlier by Key, obtained rapid fusion and reduced the total period of disability to 3 months. Eggers and his associates in 1949 fashioned a bone flap in the skull of rats bringing a portion of this flap into contact with bone of the skull with a compression force. It was noted that contact-compression favorably influenced union. Excessive pressure caused necrosis and areas not subjected to contact-compression failed to unite. The contact-compression factor was thought to stimulate osteogenesis. The compressing force was not measured but these workers believed that the most advantageous force coincided with the physiologic forces exerted by the musculature of the part involved.

If a compressing force does assist in fracture healing, it may do so by virtue of enhanced immobility of the fragments; or the beneficial effect may result from more intimate approximation and impaction of the fragments or a combination of both rigid immobility and close contact; lastly, there is the possibility that pressure may in itself stimulate osteogenesis at the fracture site.

The animal experiments reported here sought to determine if an optimum pressure range existed which would allow a fracture to heal more rapidly than when subjected to pressures in a higher or lower range. Could a curve be constructed, the co-ordinates being the rate of healing against known forces compressing the fracture site? It would be of value to compare the healing of fractures under pressures which give complete immobility and approximation with fracture healing at pressures above and below the amount necessary for such fixation and contact. No attempt was made to determine the precise amount of physiologic compression resulting from muscle tone at the particular fracture we made. However, results from compression in the grossly estimated physiologic range were compared with results from compression in the higher ranges.

## METHOD

Compression was exerted by means of calibrated springs applied across a fracture created between the proximal and middle portion of the ulnae of dogs. The distal third of the ulna was resected and it was necessary to remove the interosseous membrane to the middle fragment so that pressure could be applied effectively. Care was taken to disturb as little as possible all soft tissue attachments to

From the Department of Orthopedic Surgery, Hospital of the University of Pennsylvania, Philadelphia. This work was supported by grants from the Committee on the Advancement of Research, University of Pennsylvania and aided by the Harrison Department of Surgical Research, University of Pennsylvania.

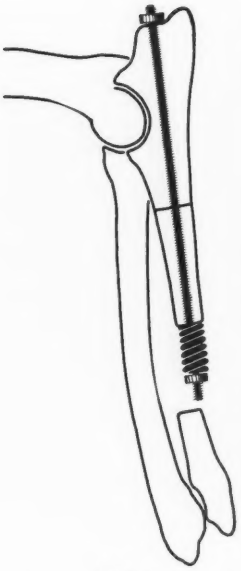

Fig. 1.

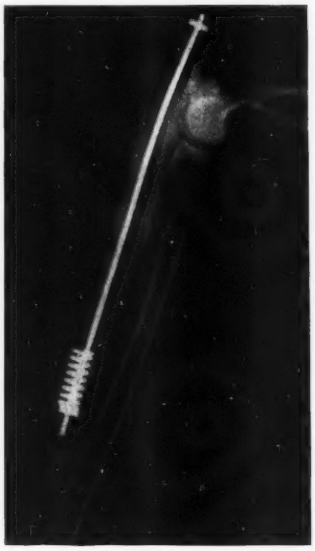

Fig. 2.

Fig. 3.

Fig. 1. Method of applying compression across a fracture created in the ulna of dogs.

Fig. 2. Bone union has occurred with little periosteal response 5 weeks subsequent to the application of a compression force of 18 pounds across the fracture.

Fig. 3. Four weeks after the application of 33 pounds across the fracture. Union was not present in spite of good impaction.

bone. A threaded stainless steel wire was inserted through the olecranon and down the medulla of the ulna. This wire crossed the fracture line at the junction of the upper and middle thirds of the ulna and was sent on completely through the middle third of the ulna and then through the calibrated spring. The wire was fixed with a nut at the olecranon and a second nut was used to tighten the spring which forced the middle fragment against the proximal. When the fracture ends were approximated without pressure, the spring was measured with calipers. Further compression of the spring as desired was accomplished and the spring length again measured. The difference between the two measurements represented spring compression acting to force the loosened middle fragment of the ulna against the proximal. The springs delivered a force of 6 pounds for each $1/32$ inch of shortening.

Four to 5 weeks after surgery roentgenograms were made and the fracture site was again exposed. The development of callus and the presence or absence of mobility was noted. The spring was again measured to note what loss of pressure had occurred and the fracture area was excised and microscopic sections made.

The initial pressure created across the fracture does not remain constant throughout the experiment. There is a known loss measured by noting the tendency of the spring to return to its original length and representing bone absorption, most of which occurred adjacent to the spring. There is also an unknown loss due to ingrowth of fibrous tissue into the spring and to fixation of the bone fragments by scar tissue.

Twenty-seven such experiments were completed. The dogs were fully grown large dogs (17 to 25 kilograms) and tolerated the procedure well. Usually they began to bear some weight on the extremity operated upon by the fourth week but as the distal third of the ulna had been resected and the interosseous membrane to the middle fragment severed, little or no weight bearing stress occurred across the fracture.

Fig. 4. Thirty pounds of pressure resulting in non-union; necrosis of cortex and absence of soft tissue in the fracture gap.

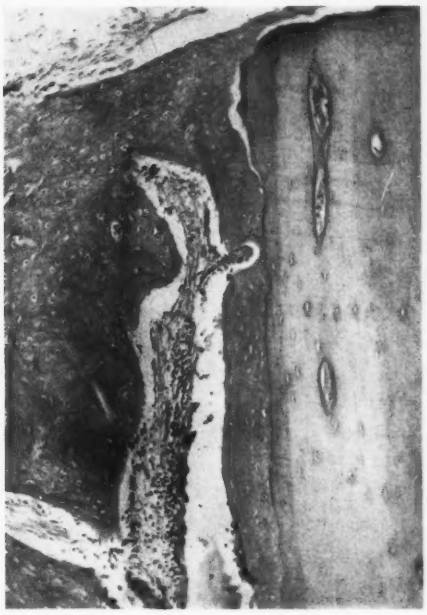

Fig. 5. An extensive inner core of medullary new bone at the fracture site which had been subjected to 12 pounds of pressure.

To permit comparison, the experiments were divided into four groups according to the amount of compression originally placed across the fracture. Pressures between 30 and 36 pounds were regarded as high; those between 12 and 18 pounds as a middle group; those between 5 and 9 as a low pressure group and those without any pressure but simply an intramedullary wire across the fracture were controls.

## RESULTS

The fractures were examined at 4 or 5 weeks after surgery. The wires were removed after the amount of lost measurable pressure was determined and the entire fracture area generously excised. Any residual mobility was classified as a failure of union. The amount of callus and disposition of the callus were noted.

In the high compression group only 1 case of union resulted in 5 experiments, this occurring in an animal that sustained a 15 pound loss of pressure (30 to 15 pounds) due to marked bone absorption adjacent to the spring. The average measured pressure lost in this group was 10 pounds. Inspection of the fractures in this group in most instances revealed scant soft tissue growth between the surfaces and reduced periosteal proliferation of tissue adjacent to the fracture.

Four cases of union occurred in 6 experiments in the intermediate group. Three of the 4 animals observed at 5 weeks had union and half of those observed at 4 weeks showed union. An average measured pressure of 6 pounds was lost.

In the low pressure group, 2 of 10 experiments went to bone union. No measurable pressure loss could be ascertained and the position of the fragments was well maintained. Soft tissue proliferation about the fracture was abundant in contrast to the sparsity of such growth in the high pressure group.

In 6 control experiments, only 1 animal developed bone union (5 weeks). The alignment in this group was adequate but not as

Fig. 6. Well developed medullary new bone in a fracture subjected to 6 pounds of pressure.

satisfactory as that observed in the other groups because of the slight transposition movements allowed the fragments on the medullary wire.

Microscopic sections in the high pressure group bore out the grossly observed findings and showed little cellular reaction in the fracture gap in most instances. The cortical bone occasionally showed degenerative changes with osteoclasis at the fracture. Both periosteal and endosteal new bone formation were observed at a distance from the fracture with the periosteal collar more predominant. This is in contrast to the findings in the intermediate pressure group which showed medullary new bone fully as abundant as the new bone on the exterior of the cortex. The endosteal new bone formation condensed along the inner surface of the cortex forming an inner core of new bone oriented along the medullary canal toward the fracture. The intermediate group also showed profuse fibrous and cartilage formation, the cartilage being localized to areas in and around the fracture gap.

Microscopic study of the fractures in the low pressure group did not differ qualitatively from the observed findings in the middle group. In most cases, the state of development of new bone was not as far advanced as that in the middle pressure group. Similarly, in the control fractures, active periosteal and endosteal bone formation was noted with islands of hyaline and fibrocartilage centered about the fracture gap.

The microscopic sections in all groups closely followed the observations of Urist and Johnson in their studies of fracture healing in long bones. The stage of the healing process varied in the different pressure groups. In the low and middle pressure group, we found very substantial endosteal new bone formation. The fractured cortical surfaces seemed to contribute cellular growth only late in the healing process. Aside from a retardation of the cellular activity adjacent to the fractured area and late necrosis of the cortical ends in the high pressure group, we could not detect microscopically any specific alteration in the process of fracture healing induced by pressure as we applied it. However, the rate of the process seemed to be influenced by compression.

Roentgenograms showed close approximation of the bone segments in most of the animals subjected to pressure. A more prominent fracture gap was seen between the fractured bone in control dogs not subject to pressure.

## DISCUSSION

Pressure across any fracture surface, whether in tubular or flat bones, is primarily borne by the cortex, whether this be well developed as in the long bones or less well developed as in the flat bones or the cancellous extremities of long bones. Bone of a resistant nature is necessary in order to exert compression. Any specific reaction to compression should be sought in this more resistant bone. In this study, apart from the necrosis of the cortical ends and the reduced cellular activity adjacent to the fracture gap which ensued under high compression, no histological deviation was noted in bone healing which could be attributed to pressure. No attempt was made to determine whether mechanical forces applied

Fig. 7. Newly deposited bone between the fractured cortices subjected to a compression force of 12 pounds. The cortices show no activity.

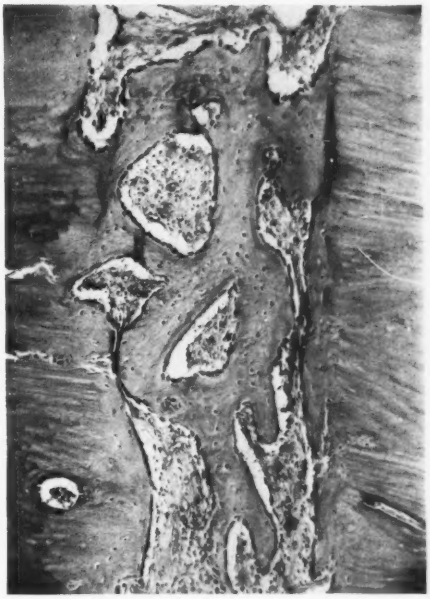

Fig. 8. Well developed new bone is shown at the fracture site in an animal which was subjected to 18 pounds of pressure.

to a fracture affected the local *p*H, phosphatase, calcium, phosphorous, or the other biochemical responses incident to a fracture.

Our present histologic concept of fracture healing in long bones as determined by Urist and Johnson places the emphasis of the healing effort on the periosteal response, while the cortices adjacent to the fracture line necrose and lose their cellular structure. The endosteum shows a more limited necrosis. The outer collar of new bone unites the fragments before the cortex is fully revascularized. Pressure then would seem to act primarily on that component of the fracture which plays a lesser role in the cellular sequence of healing.

In the middle and low pressure groups, more rapid healing was encountered than in the controls. It is possible that this resulted from rigid fixation and close bone contact. The distance to be bridged by newly growing connective tissue and bone is held to a minimum, while injury to the newly formed tissue due to movement is reduced by the firm fixation and impaction of fragments under compression. It has been shown that fractures that are firmly held in anatomic position heal with little evidence of external callus. Our observations and roentgenograms of these experimental fractures held under compression also showed less external callus and a remarkable degree of endosteal new bone formation. Such internal callus did not seem distributed in relation to the intramedullary wire.

The ordinary treated fracture in a long bone is under a compression force exerted by tonus in the muscle groups surrounding the fracture. In this study union was accelerated by increasing the pressure from 6 pounds to a range between 12 and 18 pounds. We did not attempt to determine what physiologic pressure would be exerted by muscle tone across a fracture in this area of the ulna in our animals but believe it would be inferior to the rigid bone impaction that we observed at the time of surgery even in the low pressure group. Raising the compression force to levels

TABLE I.—SUMMARY OF EXPERIMENTAL DATA

| No. | Amount of pressure applied, pounds | Time between surgery and observation, weeks | Results | Pounds of measured pressure lost |
|---|---|---|---|---|
| 1 | 5 | 4 | Fibrous union | 0 |
| 2 | 5 | 4 | Fibrous union | 0 |
| 3 | 5 | 4 | Bone union | 0 |
| 4 | 5 | 5 | Fibrous union | 0 |
| 5 | 6 | 4 | Fibrous union | 0 |
| 6 | 6 | 5 | Fibrous union | 0 |
| 7 | 6 | 5 | Fibrous union | 0 |
| 8 | 6 | 5 | Fibrous union | 0 |
| 9 | 6 | 5 | Fibrous union | 0 |
| 10 | 9 | 4 | Fibrous union | 0 |
| 11 | 12 | 4 | Fibrous union | 3 |
| 12 | 12 | 5 | Bone union | 9 |
| 13 | 18 | 4 | Bone union | 6 |
| 14 | 18 | 5 | Bone union | 12 |
| 15 | 18 | 5 | Bone union | 6 |
| 16 | 18 | 5 | Fibrous union | 3 |
| 17 | 30 | 4 | Nonunion | 0 |
| 18 | 30 | 5 | Bone union | 15 |
| 19 | 33 | 4 | Fibrous union | 9 |
| 20 | 33 | 5 | Fibrous union | 12 |
| 21 | 36 | 4 | Nonunion | 18 |
| 22 | Control | 4 | Fibrous union | .. |
| 23 | Control | 4 | Fibrous union | .. |
| 24 | Control | 4 | Fibrous union | .. |
| 25 | Control | 4 | Fibrous union | .. |
| 26 | Control | 5 | Bone union | .. |
| 27 | Control | 5 | Fibrous union | .. |

far above what the muscles were capable seemed to accelerate healing until a point was reached where cellular response lagged. We believe a curve for bone union plotted against pressure could be constructed and that the summit of the curve would occur well above physiologic pressures.

## CONCLUSIONS

1. Experimental fractures of the ulna in dogs in which a compressing force of 12 to 18 pounds was applied across the fracture showed more rapid union than those with greater or lesser pressures.

2. Pressures of 30 pounds or higher caused necrosis of the cortex and poor healing.

3. The optimum compressing force is probably above that which normally results from muscle tone.

4. Enhanced healing under pressure is believed to be related to more secure fixation and impaction of the fracture. Whether or not pressure induces a specific osteogenetic response in healing bone tissue cannot be answered.

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# STUDY OF THE ETIOLOGY OF ACUTE PANCREATITIS

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ALTHOUGH the clinical and gross pathological picture of acute pancreatitis is well recognized by surgeons, the etiology of this disease is poorly understood. Of the many theories evolved from clinical and experimental studies, one (9) suggests that duct obstruction in an actively secreting pancreatic gland may result in acute pancreatitis. To test this hypothesis studies were carried out on dogs by stimulating the pancreas with pancreozymin, a known physiological stimulant, after complete ligation and division of the pancreatic ducts. Another theory (10) indicates that temporary compromise of the arterial blood supply to the gland in addition to duct obstruction may produce changes simulating pancreatic necrosis. An indirect evaluation of this theory was made by introducing an oily emulsion into the arterial blood of the pancreas after ligation and division of the ducts. The studies included fluctuations in the serum amylase and lipase levels in addition to gross and microscopic changes in the pancreas.

## EXPERIMENTAL

The determinations of serum amylase and lipase were begun 20 minutes after collection of the blood by jugular venipuncture. The serum amylase levels were obtained by incubating 1 milliliter of the serum with starch paste and determining the glucose by the copper reduction method and titration with standard sodium thiosulfate. The serum lipase levels were measured by using the Johnson and Comfort modifications of the original method of Cherry and Crandall. An olive oil substrate was used with tergitol 7® added as an emulsifier. The end results were expressed in units representing the number of milliliters of N/20 sodium hydroxide required for the neutralization of the fatty acid liberated by 1 milliliter of the serum.

The pancreozymin was prepared from hog intestine by the method described by Harper and Raper (6). Instead of scraping the first 5 feet of small intestine to remove the duodenal mucosa, the entire segment—the proximal 5 feet of small intestine—was placed in solid carbon dioxide at the slaughter house, ground in the frozen state, and added to alcohol. The alcohol extract was worked up as described by Harper and Raper. The yield of pancreozymin was 50 milligrams of "alcohol-soluble" material per 100 grams of tissue or about one-third that of the original investigators. Assay of the product, by injecting it with secretin intravenously into dogs anesthetized with sodium pentobarbiturate and collecting the pancreatic juice through a plastic cannula, showed a twofold increase of the pancreatic juice amylase during a 10 minute collection period. This value was obtained when the pancreozymin was given at the dosage of 2 milligrams per kilogram of body weight. In contrast, Harper and Raper reported a threefold increase for 1 milligram per kilogram of body weight.

Young, healthy, mongrel dogs were used in the studies. Serum amylase and lipase levels were determined 24 hours prior to surgery. Using intravenous sodium pentobarbiturate anesthesia and sterile technique, the abdomen was opened through an upper right rectus muscle-splitting incision. By careful dissection the pancreas was partially separated from the duodenum to insure location of all of the ducts. The usual number and location of the ducts are shown in Figure 1. Each duct was isolated, divided between stitch ties of fine silk; the proximal stump was inverted into the duodenum, and the distal stump into the gland. The incision was closed in layers

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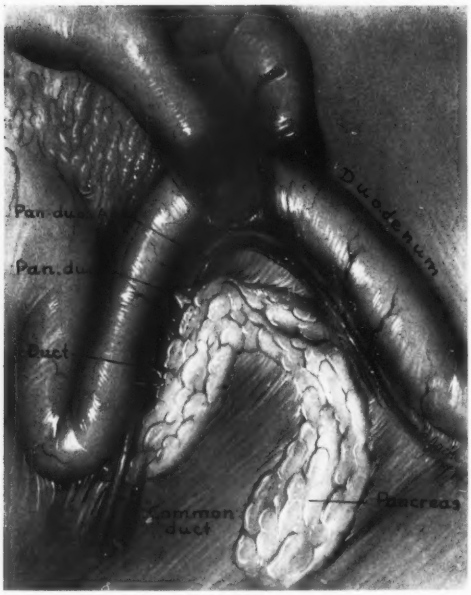



Fig. 1. Drawing showing the usual number and location of the pancreatic ducts in the dog.

with interrupted silk sutures. On the first postoperative day the animal was allowed to eat, and blood was withdrawn for chemistries. The latter procedure was repeated every other day. On the third postoperative day the dogs were re-explored for evidence of pancreatitis. After 14 days, all of the dogs were sacrificed and postmortem studies were carried out.

To evaluate the theory that ductal obstruction in an actively secreting gland will result in acute pancreatitis, two series of dogs were operated upon. In the first group of 5 animals the ducts were ligated and the animals were allowed to eat on the first postoperative day. It was assumed that changes in the serum enzyme levels were the result of the stimulation of the pancreas by food. In the second group of 5 animals the ducts were similarly ligated, but at the termination of the operative procedure the gland was stimulated by the intravenous injection of secretin and pancreozymin. The dosage of pancreozymin was 2 milligrams per kilogram of body weight. On the first and second postoperative days the same dosage of the "alcohol-soluble" preparation was given 3 times in 24 hours, and on the third and fourth days 2 times in 24 hours.

Temporary compromise of the arterial blood supply to the pancreas was obtained by gently exposing the superior pancreaticoduodenal artery just before it enters the pancreas, and by injecting 4 milliliters of an oily radiopaque emulsion (particle size 3 to 5 microns) through a fine needle. Roentgenograms made 1 hour after injection showed that some of the medium remained in the vessels. One group of dogs was treated in the manner described. Another group of 5 dogs was similarly treated except that the oily emulsion was injected after the pancreatic ducts had been ligated. Postoperatively, the dogs were studied as in the previous experiment except that in the last group of 5 dogs serum lipase determinations were not performed.

## RESULTS

The group of dogs subjected to ductal ligation and immediately allowed to eat postoperatively showed changes in the blood serum amylase and lipase levels illustrated in Figure 2a. Only 3 dogs in which successful duct ligation was achieved are included in the chart. The chart shows sudden elevations in the serum amylase levels which drop within 5 days and by 2 weeks have reached the preoperative levels. The serum lipases were slower in rising but remained up after the amylase levels had receded. Exploratory laparotomy on the third postoperative day revealed only moderate edema of the pancreas. At necropsy, there was considerable atrophy of the gland with mild inflammatory reaction and fibrosis. Microscopically, considerable acinar atrophy had occurred with interlobular fibrosis and chronic inflammatory cell infiltration (Fig. 3a).

Changes in the serum enzyme levels in the dogs stimulated with pancreozymin following duct ligation are represented in Figure 2b. Four dogs in this group were successfully ligated. Here the amylase and lipase levels were higher but tended to follow the same pattern as the previous group. On the third postoperative day the gland showed only marked edema. Postmortem examinations

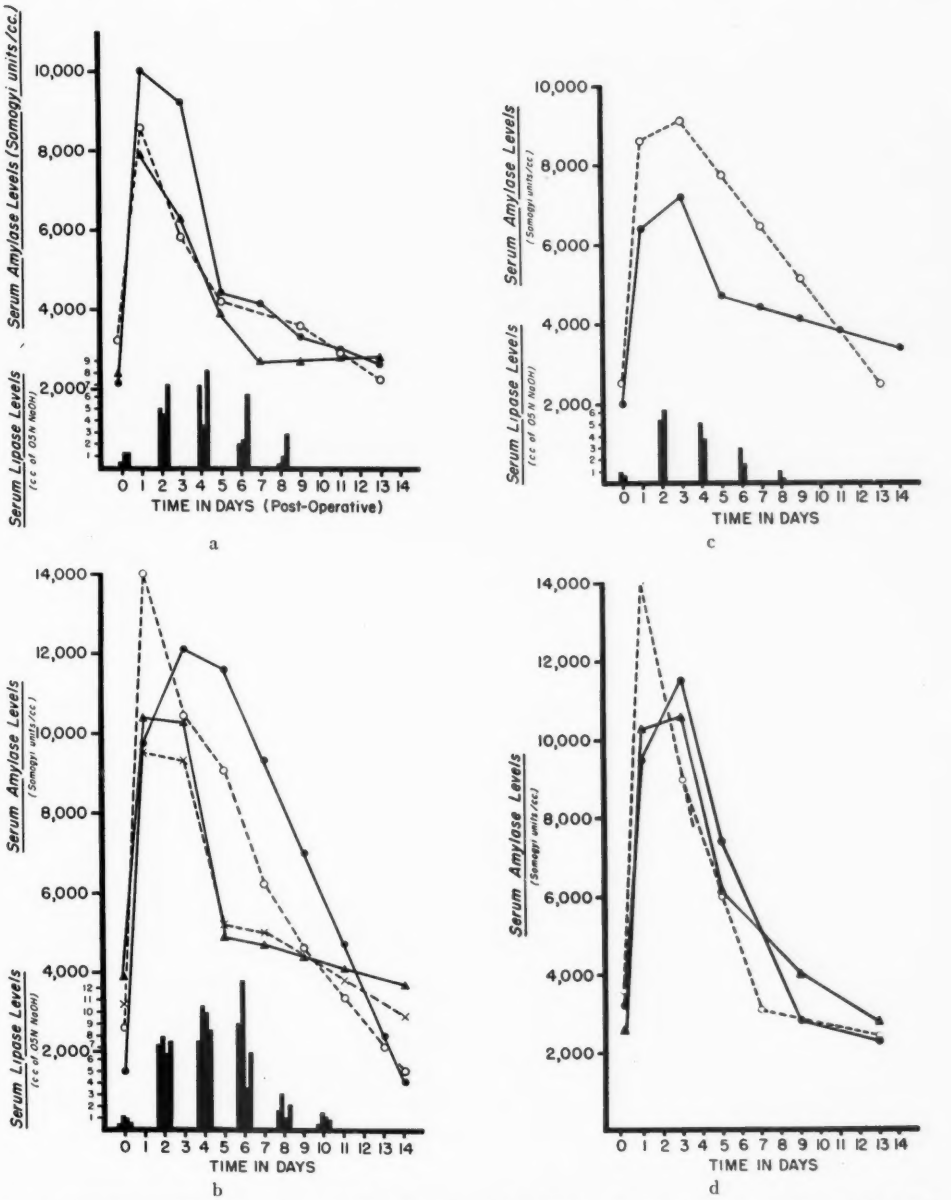
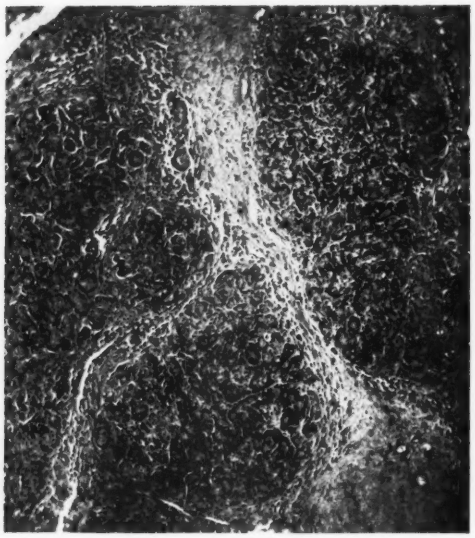



Fig. 2. Graphic representation of serum amylase and lipase levels: a, with pancreatic duct ligation and normal dietary stimuli; b, with pancreatic duct ligation followed by stimulation with pancreozymin and secretin over a period of 4 days; c, without ligation but following injection of the superior pancreaticoduodenal artery with 4 milliliters of an oily emulsion; and d, with ligation of the pancreatic ducts and following the injection of the superior pancreaticoduodenal artery with 4 milliliters of an oily emulsion.



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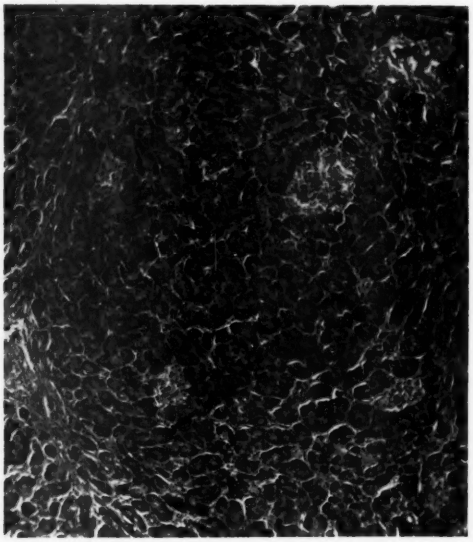

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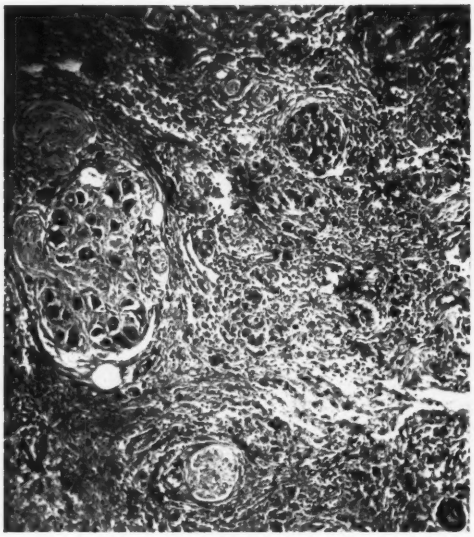

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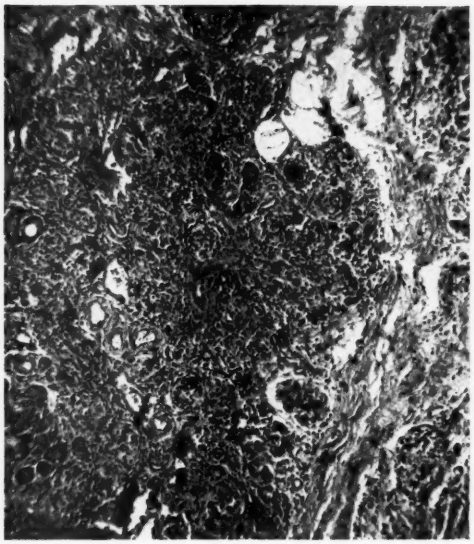

d

Fig. 3. Stained sections of the dog's pancreas: a, following duct ligation and normal dietary stimuli, atrophy of the acinar tissue with interlobular fibrosis and small round cell infiltration is seen; b, following duct ligation and stimulation with pancreozymin and secretin over a 4 day period, complete atrophy of the acinar tissue is noted together with fibrous tissue replacement and the presence of acute and chronic inflammatory cells; c, following the injection of 4 milliliters of an oily emulsion without duct ligation, normal architecture is seen; and d, following duct ligation and the injection of 4 milliliters of an oily emulsion, almost complete atrophy of the acinar tissue is evident together with marked inflammatory cell infiltration and interlobular fibrosis.

revealed increased inflammatory reaction and atrophy. Two dogs showed some very small areas of fat necrosis in the area of the ligation of the main duct. In the stained sections, almost complete atrophy of the acinar tissue was seen with considerable interlobular fibrosis and acute and chronic inflammatory cell infiltration (Fig. 3b).

In 2 dogs with patent ductal systems, injection of the superior pancreaticoduodenal artery with 4 milliliters of an oily emulsion resulted in only a moderate rise of the serum amylase and lipase levels (Fig. 2c). There was very little gross change in the gland, and microscopically the architecture of the acinar tissue appeared undisturbed (Fig. 3c). In marked contrast, the 3 dogs in which successful duct ligation was achieved and the artery injected with the emulsion, the elevations in serum enzyme levels were considerable (Fig. 2d). The extent of rise and the pattern closely simulates that seen in the group stimulated with pancreozymin after ligation of the ducts. However, at exploratory laparotomy only 1 of the 3 dogs showed slight evidence of fat necrosis in one area of the gland. Necropsy studies revealed marked atrophy, fibrosis, and chronic inflammation. Microscopically, only marked atrophy, interlobular fibrosis, and small round cell infiltration were present (Fig. 3d).

## DISCUSSION

Secretin, first isolated by Mellanby, results in an increased flow of pancreatic juice, consisting chiefly of water and sodium bicarbonate. Pancreozymin affects the external secretory activity of the pancreas by causing an increase in the output of the pancreatic enzymes in the juice, when given with secretin. Isolation of this hormone was achieved by Harper and Raper (6), and their original work was substantiated by Greengard, Grossman, Woolley, and Ivy. Histological studies on the rat pancreas showed that administration of the hormone produced a washing out of the secretory granules of the pancreatic acinar tissue very similar to changes produced by vagus nerve stimulation (7). Following the ingestion of food, acid chyme entering the duodenum influences the pancreas to secrete fluid high in enzyme content (11).

Utilization of these two potent stimuli in the presence of complete duct obstruction in dogs resulted in very high serum amylase and lipase levels, but gross and histological studies did not yield any evidence to indicate that acute pancreatitis, as manifested by fat and hemorrhagic necrosis, was produced. Similarly, duct obstruction followed by the introduction of fat emboli into the arterial blood supply of the gland produced clinical evidence of acute pancreatitis, but no fat necrosis or necrotizing hemorrhage.

Evidently, other factors must be involved in the production of acute pancreatitis. Work in progress suggests dietary imbalance to be one of the most important. Pancreatitis may be produced readily in the dog by administration of d,l-ethionine, a presumed antagonist of the essential amino acid methionine. Small doses of the drug of the order of 25 milligrams per kilogram of body weight, administered daily to dogs over a period of several weeks, result in extensive atrophy of the pancreas, whereas larger doses of 150 to 200 milligrams per kilogram over a period of 8 to 10 days produce pancreatitis with extensive fat necrosis and hemorrhagic areas. The serum amylase levels do not rise, but tend to fall. In addition to the acinar degeneration of the pancreas, fatty changes occur in the liver. The administration of d,l-ethionine induces changes in the pancreas of the dog that are more varied than those reported in the rat (3, 4).

## CONCLUSIONS

After ligation of the pancreatic ducts in dogs, stimulation of the gland by food, or by food and the intravenous administration of secretin and pancreozymin, resulted in immediate elevations of serum amylase and lipase levels. Similarly, high serum enzyme levels were found after duct ligation and the injection of an oily emulsion into the arterial blood supply of the pancreas. Although the changes in the serum enzyme levels simulate the clinical picture of acute pancreatitis, no fat or hemorrhagic necrosis was found. The latter changes may be produced, without serum enzyme elevation, by the oral administration of d,l-ethionine.

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## AN EVALUATION OF THE CYTOLOGIC EXAMINATION OF BODY SECRETIONS IN THE DIAGNOSIS OF CANCER

SINCE Papanicolaou's contribution[1] on the identification of cancer cells in vaginal smears, practically every secretion and orifice of the body has been investigated by his smear method or variants of it. The various materials which have been studied include vaginal material, sputum and bronchial secretions, esophageal material, gastric washings, feces, spinal fluid, urine, and secretions from the breast. Initially much enthusiasm was displayed concerning the value of cytologic diagnosis in many of these fields but it is becoming evident that this method of diagnosis is of much more value in certain fields than others. The smear technique has proved most useful in the diagnosis of carcinoma in situ of the cervix and pulmonary carcinoma. The reasons for the usefulness in these two fields are different. Carcinoma in situ of the cervix seldom has any gross features which will distinguish it from other commoner lesions such as erosion. On the other hand, while primary pulmonary carcinoma is a characteristic lesion grossly, the organ is not readily accessible for diagnostic purposes.

A cytologic laboratory, in order to attain maximal efficiency, probably should be organized with the aid of technician scanners who have had adequate training in the recognition of cancer cells in smears. It is not possible for a pathologist to spend the necessary amount of time needed in scanning unknown material. The cytologist need only review those cells which appear suspicious to the technician and render the final opinion. It is also necessary for the cytologist to check the technician's negative results occasionally. For a physician to be a pathologist does not mean that he is a cytologist. To be a competent cytologist, it is necessary for a pathologist to spend hours in self-training. Because of the time-consuming nature of existing cytologic methods, the procedure is a costly one which is done adequately in only a few centers. It is possible that new methods such as the microfluorometric method being studied by Mellors, Papanicolaou, and Glassman[2] will lessen the time factor needed for human scanning and thus make the procedure a sounder one economically.

The two stains which have been most commonly employed in the cytologic diagnosis of cancer are the Papanicolaou stain and hema-

[1]PAPANICOLAOU, G. N. New cancer diagnosis. Proc. Third Race Betterment Conference, 1928, p. 528.

[2]MELLORS, R. C., PAPANICOLAOU, G. N., and GLASSMAN, ADELE, (Abstr.) A microfluorometric method under development for the scanning and the detection of cancer cells in vaginal smears Am. J. Path., 1951, 27: 734–735.

toxylin and eosin stain. There is little to choose between them. The accuracy of the test does not depend as much on the stain which is employed as it does on the experience of the examiner. It still remains a fact that there is no specific stain for cancer cells such as there is for the tubercle bacillus.

Studies of urinary smears and prostatic secretions have led to somewhat variable results. Botsford and Tucker[3] claim that urinary smears and vaginal smears are the two most practical ones for cytologic examination. Hock, Wood, and Kosinski[4] were able to make a diagnosis of carcinoma of the prostate in 30 per cent of cases of proved carcinoma in a small series of cases. McDonald's experience[5] would indicate that urinary smears can be utilized to make a diagnosis of the more anaplastic types of carcinoma of the bladder but are of very little use in the less malignant papillary varieties. Such smears are of questionable value in competition with a competent cystoscopist. In carcinoma of the kidney, examination of urinary sediment produces too many false positive errors and too many false negative errors to be of practical value. In the examination of prostatic smears, cytologic methods of diagnosis are very accurate when the results are positive. However, the percentage of cases in which there is a single nodule deep in the prostate and in which positive results are obtained with prostatic smears is very low. It is in this type of case that the lesion is most amenable to surgical excision. Furthermore, the procedure of prostatic massage is not a recommended one for carcinoma of the prostate. It would appear that the procedure has limited value here.

The cytologic examination of gastric washings has led to disappointing results. Seybolt, Papanicolaou, and Cooper[6] reported that they were able to obtain positive results in 32.8 per cent of a series of 168 carcinomas of the stomach while the false positive error was 2.5 per cent. The experience of Swarts, Ragins, Bernstein, and Meyer[7] and of Bryant, Craig, and Pollard[8] is similar to that of the above workers. It is possible that the method of dissolving the mucus in the stomach by papain as suggested by Rosenthal and Traut[9] will lead to a practical method for increasing the number of positive results that can be obtained in cases of carcinoma of the stomach. The method of Andersen, McDonald, and Olsen[10] by which direct smears of esophageal and cardiac lesions of the stomach are taken through the open end of the esophagoscope has proved to be a valuable adjunct in diagnosis. This can be particularly valuable in lesions of the cardiac end of the stomach.

The cytologic examination of sputum and bronchial secretions has been utilized extensively in a few centers. McDonald has found that in 1,000 consecutive positive diagnoses of carcinoma based on the examination of both sputum and bronchial secretions he has had only 10 false positive reports. It is very difficult if not impossible to determine how many cancers of the lung cannot be diagnosed by the examination of sputum and bronchial secretions, but it would appear that in 30 to 40 per cent of cases of bronchogenic carcinoma

[3]Botsford, T. W., and Tucker, Martha R. Application of cytologic smear methods to cancer diagnosis in a general hospital. J. Am. M. Ass., 1950, 142: 975–979.

[4]Hock, E. F., Wood, F. W., and Kosinski, A. A. The cytologic detection of prostatic carcinoma: its clinical application. J. Urol., Balt., 1950, 63: 1081–1085.

[5]McDonald, J. R. Unpublished data.

[6]Seybolt, J. F., Papanicolaou, G. N., and Cooper, W. A. Cytology in the diagnosis of gastric cancer. Cancer, 1951 4: 286–295.

[7]Swarts, J. M., Ragins, A. B., Bernstein, Arthur, and Meyer, Jacob. Diagnosis of gastric cancer by cytologic examination of gastric washings. Gastroenterology, 1950, 14: 265–274.

[8]Bryant, H. C., Craig, W. R., and Pollard, H. M. Cytologic study of gastric aspirate for carcinoma cells. J. Nat. Cancer Inst., 1949, 10: 459–466.

[9]Rosenthal, M., and Traut, H. F. The mucolytic action of papain for cell concentration in the diagnosis of gastric cancer. Cancer, 1951, 4: 147–149.

[10]Andersen, H. A., McDonald, J. R., and Olsen, A. M. Cytologic diagnosis of carcinoma of the esophagus and cardia of the stomach. Proc. Mayo Clin., 1949, 24: 245–253.

cancer cells are not present in the sputum. This high figure does not mean that the procedure is worthless; on the contrary, the lung is a relatively inaccessible organ and other means of positive diagnosis short of thoracotomy are notoriously poorer than those of pulmonary cytology.

In the gynecologic field the cytologic smear has its most practical application in the discovery of preclinical carcinoma of the uterine cervix. Fundal carcinoma, evasive to the cytologist, is much less common and less lethal than cervical carcinoma. When gynecologic carcinoma is manifest or clinically suspected, more conventional diagnostic measures are preferable.

The average age at which cervical carcinoma in situ is detected is in the latter part of the fourth decade, at an age about ten years younger than that for the symptomatic lesion. If the assumptions are true, as an increasing number of students of the subject believe, that intraepithelial carcinoma usually goes on to invasion and that the invading lesions usually have had an intraepithelial phase, this 10 year delay offers a unique opportunity to the cytologist.

It has been amply demonstrated that a single properly prepared cervical smear is more accurate in the detection of preclinical carcinoma than is a single conventional biopsy specimen, chiefly because the lesion is so often not grossly apparent.[11]

In screening smears from "noncancerous" appearing cervices, between 0.5 and 1.0 per cent of such smears reveal an unsuspected cervical carcinoma which is usually preinvasive. Cervical smears have become a valuable adjunct in the detection of early carcinoma.

JOHN R. MCDONALD
DAVID C. DAHLIN

[11]DAHLIN, D. C., MUSSEY, ELIZABETH, and DOCKERTY, M. B. Cervical smears in the detection of preclinical carcinoma: our experience with 10,000 cases. Unpublished data.

## ESOPHAGEAL BLEEDING

THE most common cause of bleeding from the esophagus is hemorrhage from ruptured esophageal varices. Although peptic ulcer is by far the most common cause of massive upper gastrointestinal bleeding, hemorrhage from esophageal varices accounts for from 5 to 20 per cent of the cases in most reported series and usually ranks in second place. The mortality rate of patients with bleeding esophageal varices ranges as high as 60 to 70 per cent. Patek and his associates[1] found that approximately 50 per cent of patients who have hemorrhage from esophageal varices die within 1 year after the first hemorrhage.

Esophageal varices represent one of the collateral channels which develops between the portal and systemic venous systems when some type of chronic obstruction to the flow of blood through the portal system has resulted in an increased portal venous pressure. In approximately 95 per cent of such cases the obstruction will be the so-called intrahepatic type which results from cirrhosis of the liver. The remaining cases result from an extrahepatic obstruction and usually present a clinical picture compatible with the diagnosis of Banti's disease. Thrombosis of a major segment of the portal system is the usual source of extrahepatic obstruction although cavernous transportation of the portal vein, aneurysm of the splenic artery, and other rare etiological conditions have been reported. An increased number of engorged veins are frequently seen along the upper gastrointestinal tract in cases of portal hypertension and bleeding from submucosal veins in the fundus of the stomach may be associated with bleeding from esophageal varices. The loosely supported eso-

[1]PATEK, A. J., JR., POST, JOSEPH, RATNOFF, OSCAR D MANKIN, HAROLD, and HILLMAN, ROBERT W. Dietary treatment of cirrhosis of the liver. J. Am. M. Ass., 1948, 138: 543.

phageal veins, protected by only a thin layer of mucosa and subjected to the constant change of intrathoracic pressures during respirations, undergo considerable dilatation with consequent vulnerability to rupture. The mechanism whereby rupture occurs is poorly understood, but there is evidence to suggest that ulceration produced by regurgitated gastric juice is the most important factor.

The diagnosis of a Banti's disease type of extrahepatic obstruction in the case of massive upper gastrointestinal hemorrhage may be suggested by the age of the patient, as hematemesis frequently occurs in these cases during childhood or early adult life. The presence of splenomegaly, anemia, and, at times, leucopenia and thrombocytopenia strongly suggests a diagnosis of Banti's disease.

Bleeding from esophageal varices secondary to cirrhosis of the liver usually presents a more difficult diagnostic problem. The age of these patients corresponds closely to the age of patients bleeding from peptic ulcer. Approximately 50 per cent of both groups are 40 to 60 years old. Males predominate in both groups. However, whereas males comprise 90 to 95 per cent of the bleeding ulcer patients, they make up only 60 to 65 per cent of the group with bleeding esophageal varices. Bleeding from varices comes on suddenly, is painless, and may be the first indication of the patient's illness. The majority of patients with bleeding varices and cirrhosis are chronic alcoholics. Bleeding may occur during an acute phase of the cirrhotic process, and signs of acute hepatic insufficiency will immediately suggest the diagnosis. In such a case there may be a history of marked recent anorexia, nausea, weakness, and general malaise. Jaundice, ascites, and enlargement of the liver and spleen are usually present. Spider angiomas of the skin and palmar erythema are frequently present and are fairly characteristic of cirrhosis. The total serum proteins and serum albumin are reduced. The prothrombin time is markedly prolonged. The cephalin flocculation and thymol turbidity tests are positive, and other liver tests indicate a marked hepatic insufficiency. Such an acute phase not infrequently follows closely upon an alcoholic spree.

Bleeding which occurs during a quiescent phase of the cirrhotic process presents the most difficult diagnostic problem and the one which must be differentiated most frequently from a bleeding peptic ulcer. The absence of ulcer symptoms both immediately preceding the bleeding episode and prior to this time points toward a diagnosis of esophageal bleeding. However, the most important diagnostic signs are the presence of an enlarged hard liver, possibly an enlarged spleen, and evidence of superficial collateral circulation. Signs of impaired liver function, although not as marked as during the acute phase of cirrhosis, will be present. If the patient's condition permits, and the diagnosis cannot be satisfactorily determined otherwise, an x-ray examination after the ingestion of barium is indicated to permit careful inspection of the esophagus, stomach, and duodenum. Positive x-ray findings are exceedingly helpful. However, bleeding varices may be present even when they cannot be demonstrated. After bleeding has stopped, an esophagoscopic examination may be carried out.

The emergency treatment of bleeding esophageal varices once the diagnosis has been established may be outlined as follows: (1) adequate blood replacement; (2) supportive hepatic therapy, particularly for episodes of bleeding during a phase of acute hepatic failure; (3) discontinuation of oral intake during active bleeding; and (4) esophageal tamponade.

Early and adequate blood replacement is essential. Intravenous fluids other than blood

may be used sparingly at the time of admission until compatible blood is available; then approximately 1,500 cubic centimeters per 24 hours should be administered to care for insensible fluid loss and urinary function while transfusions are being given. The rate of bleeding may be rapid in this type of hemorrhage, and massive continued blood administration may be required. Four to eight thousand cubic centimeters of blood may be required within a 24 hour period.

Caution must be exercised in the administration of drugs to produce sedation if impaired liver function is suspected.

If there are signs of acute hepatic insufficiency, the parenteral administration of vitamin K is indicated. Oral intake is discontinued during the bleeding period, but liquids and bland foods are usually started 12 hours after bleeding has stopped.

In the event of continued copious bleeding, esophageal tamponade should be applied. The preferred method consists of passing a multiple lumen tube which has two separately inflatable balloons—a smaller balloon on the distal portion of the tube which is passed through the esophagogastric orifice and a proximal balloon which is inflated in the lower end of the esophagus. Patton recommends deflating the upper balloon at the end of 12 hours. If there is evidence of bleeding, the balloon is reinflated for an additional 12 hour period.

It has been suggested that an emergency blood vessel shunt operation may be indicated at times if bleeding persists. However, the mortality rate of such operative treatment is, at present, prohibitive. After the acute bleeding episode has passed, consideration must be given to measures which may prevent a recurrence. Those patients with a marked acute depression of hepatic function may experience considerable improvement from prolonged rest, a high carbohydrate, high protein, high vitamin diet, and abstinence from alcohol. If portal hypertension is present, operative treatment may be considered after hepatic function has reached maximum improvement.

Of the numerous types of operative procedures which have been devised for the treatment of portal hypertension, the two that are most strongly advocated at present are (1) the portacaval shunt operations of Blakemore[2] and (2) esophagogastric resection. In certain carefully selected cases, splenectomy has been beneficial. Ligation of the splenic and hepatic arteries as suggested by Rienhoff[3] and Berman and his associates[4] may be expected to lower the portal venous pressure. Whether the indirect lowering of the pressure by arterial ligation will be as effective as the more direct method of venous shunt or whether the effect of arterial ligation will be abolished as collateral circulation develops is a question which cannot be answered at the present time. In general, the use of the venous shunt procedures has been favored. In cases of extrahepatic Banti's type of illness with an enlarged spleen, a splenectomy and end-to-side splenorenal anastomosis is indicated. There are two chief reasons for selecting this approach: (1) removal of the enlarged spleen is beneficial in abolishing the effects of hypersplenism, and (2) the portal vein is frequently unsuited for anastomosis in these cases because of thrombosis, fibrosis, or other defects.

For the intrahepatic type of obstruction such as occurs in cases of cirrhosis, the side-to-side portacaval anastomosis is now strongly favored. A larger anastomosis can be established with this procedure, and the incidence of postoperative thrombosis at the site of the

[2]Blakemore, A. H. The portacaval shunt in the surgical treatment of portal hypertension. Ann. Surg., 1948, 128: 825.

[3]Rienhoff, William F., Jr. Ligation of the hepatic and splenic arteries in the treatment of portal hypertension with a report of six cases. Bull. Johns Hopkins Hosp., 1951, 88: 368.

[4]Berman, J. K., Koenig, H., and Saint, W. K. Ligation of the hepatic and splenic arteries in the treatment of portal hypertension. Q. Bull. Indiana Univ. M. Center, 1950, 12: 99.

anastomosis should be reduced. Also, the numerous collateral vessels around the spleen may be left intact. The formerly used end-to-side portacaval anastomosis has been abandoned, as it seems quite certain that complete interruption of the portal blood flow through the liver contributes to a fatal postoperative hepatic insufficiency in some patients. For the portacaval or splenorenal anastomosis, a long right or left incision over the costal margin is used with division of the costal margin and the ends of the sixth, seventh, and eighth ribs. A costal margin flap is then reflected upward. This procedure gives adequate exposure of the upper quadrants without opening into the thorax.

In a limited number of cases in which bleeding could not be adequately controlled by a shunt procedure, esophagogastric resection has been performed. This procedure removes the region of the esophagus in which varices are most frequently located and interrupts the flow of portal blood through the vulnerable collateral venous channels of the esophagus. In one such case a secondary total gastric resection was necessary in order to abolish bleeding from engorged vessels in the gastric remnant.

Acute esophageal hemorrhage from sources other than varices is unusual. Bleeding from esophagitis or peptic ulcer of the esophagus is rarely of the massive type unless a major vessel, such as the pulmonary artery or aorta, is eroded. In such cases the hemorrhage is usually fatal within a very short period of time regardless of therapy. In about 3 per cent of the cases of carcinoma of the esophagus, hematemesis occurs as a result of erosion of the growth into an esophageal vessel. Conservative treatment during the bleeding episode with a subsequent excision of the involved esophagus, if possible, is indicated in these cases. Perforation of an aortic aneurysm into the esophagus occurs in rare instances, and bleeding is usually fatal within a short period of time. The diagnosis is usually suggested by the shadow of the aneurysm in a roentgenogram of the chest. Other rare causes of esophageal bleeding include hemorrhage from an esophageal diverticulum, from esophagitis associated with cardiospasm, and from foreign bodies lodged in the esophagus. After bleeding has stopped and the blood volume restored by transfusions, surgical treatment of the primary disease is indicated.

WILLIAM P. LONGMIRE, JR.

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## REVIEWS OF NEW BOOKS

IN his monograph *Topographische Ausdeutung der Bronchien im Roentgenbild*[1] Dr. Esser has provided the medical profession with a valuable reference book on bronchial anatomy. It will be of greatest interest to phthisiologists, bronchoscopists, and thoracic surgeons.

As stated in his introduction, Dr. Esser has attempted to present a detailed study of the morphology of the bronchial tree, correlating it with roentgenographic studies including tomograms, bronchograms, and routine roentgenograms. The pathology and physiology of the bronchial tree are not stressed. The material for this work was obtained from numerous studies carried out at the University Institute for Roentgenology and Radiology of the Charity Hospital, Berlin; the Roentgen Department of the Caritas Hospital, Köln-Hohenlind; and the University-Roentgen Institute, Mainz.

The first part of the book deals with the over-all plan of the course of the bronchi, the historical aspects of bronchial anatomy, investigative methods, nomenclature and the form of bronchial and vascular pathways. In the section on nomenclature the author reviews in detail the work of other men in the field and points out advantages and shortcomings of earlier and current terminologies. He himself adheres to the systems of nomenclature advanced by Jackson and Huber, Overholt, and Boyden, with a few minor exceptions.

The major portion of the 152 page monograph deals in a meticulously detailed fashion with the anatomy of the bronchi and their branches. Each bronchus and its branches are discussed fully under the following headings: origin, variations, course, individual characteristics, blood vessels, roentgenographic appearance, branches, and destination. For purposes of clarification, the author presents at the beginning of each discussion a list of the various names used by other workers for the particular bronchus in question.

The whole is profusely and beautifully illustrated with diagrams, bronchograms, tomograms, and routine roentgenograms taken in various projections. A valuable aid to the reader is the use, with each roentgen study, of a diagram depicting the projection in which the film was made.

If any criticism can be offered, it would be that the work contains an excess of detail. It is unlikely that the thoracic surgeon will find this book of great practicality for everyday clinical use. However, it will serve as an excellent reference work on the structure and roentgenographic appearance of the bronchial tree. F. HENRY ELLIS, JR.

[1]TOPOGRAPHISCHE AUSDEUTUNG DER BRONCHIEN IM ROENTGENBILD MIT BERUECKSICHTIGUNG DER NEUZEITLICHEN NOMENKLATUR. By Priv.-Doz. Dr. C. Esser. Stuttgart: Georg Thieme, 1951.

THE first edition of the book *Die Behandlung entzündlicher Genitalerkrankungen der Frau*[2] appeared in 1932 and the second one in 1946. The book deals with inflammatory diseases of the female genital tract. The author discusses the etiology and spread of pelvic inflammations, the diagnosis, and treatment. The following organs are considered in the order given here: vulva, vagina, cervix, corpus uteri, adnexa, peritoneum, and pelvic connective tissue. A special chapter is devoted to the treatment of gonorrhea and genital tuberculosis.

Throughout the book, the author recommends both simple and elaborate prescriptions and many drugs which are not used in the United States. Of course, he discusses chemotherapy and the antibiotics, especially for gonorrhea and pelvic tuberculosis. For the former, the author recommends penicillin and the sulfonamides. He emphasizes that chemotherapy in pelvic tuberculosis cannot replace the customary therapy but should be used only as supportive treatment. At least 9 to 12 months are required to determine a cure of tuberculosis.

The book contains a great deal of useful information, but it is safe to predict that if a fourth edition should appear, it will be much smaller than the present volume because of the simplification of therapy of pelvic inflammatory disease by chemo-antibiotic therapy. Because of the innumerable references to therapy with unfamiliar drugs, this book will not be helpful to American physicians, but it is popular in Germany. J. P. GREENHILL.

THE monograph *The Temporomandibular Joint*[3] is one of a series entitled the "American Lectures in Dentistry" and is concerned with the syndrome of clicking and chronic pain emanating from the temporomandibular joint.

The sections on gross and minute anatomy, development, and on normal and abnormal functioning of the area are well presented in considerable detail. The remainder of the book is concerned largely with

[2]DIE BEHANDLUNG ENTZÜNDLICHER GENITALERKRANKUNGEN DER FRAU. By Prof. Dr. Gustav Döderlein. 3rd ed. Leipzig: Georg Thieme, 1951.

[3]THE TEMPOROMANDIBULAR JOINT. Edited by Dr. Bernard G. Sarnat, M.S., M.D., D.D.S., F.A.C.S. Springfield, Ill.: Charles C. Thomas, 1951.

the pathogenesis, diagnosis, and dental treatment of this condition. From the arguments presented, it would appear that certain aspects of these are still controversial.

Though primarily dental in scope and focus, the book contains much information which is useful and of interest to surgeons who have contact with this work. FRANK MCDOWELL.

THE first edition of *Heart Disease*[1] was published in 1931, twenty years ago. The popularity of the first, second, and third editions imply the excellence of the fourth. The new features of particular interest include the recent advances in the field of cardiac surgery in congenital heart disease and Dr. White's views on surgery for hypertension. He presents a conservative attitude toward the use of anticoagulants in coronary disease.

The book is well organized, legibly printed, nicely illustrated, and accurately indexed. The bibliographies are unusually good. CHAUNCEY C. MAHER.

THERE is probably nothing in the medical literature in the English language that is comparable to the exhaustive new French text on general surgery, *Traité de thérapeutique chirurgicale*[2] written by two surgeons of the Faculté de Médecine, in Lyon, France. It comprises almost 3,400 pages of close print, without a single illustration, and it deals with all phases of matters surgical from the subjects of anesthesia, infections, trauma, and those matters considered in this country to be the concern of the bone and joint surgeon, through all the subjects common to the general surgeon, to a long consideration of gynecologic and urologic subjects. Thoracic and neurologic surgery are included, and in all sections there is a special interest in the subject of tumors.

In creating this tremendous work, the authors had in mind certain specific attainments which would make their book entirely different from the usual text on general surgery. The book is, indeed, intended for the use of students, doctors beginning in practice, and already competent general surgeons, but they have made special effort to avoid discussions or explanations of actual surgical technique. Rather, they have discussed etiology, the rationale for various avenues of treatment, indications for the special methods of certain authors, to whom they freely refer, the anatomical and physiological bases for the various forms of surgical treatment according to the pathology, diagnostic difficulties, complications to be expected, and results that are of common experience. The range of subjects discussed is most exceptional.

No bibliography is furnished, and the authors state that they have purposely omitted one because to have included even an extensive one would undoubtedly have been to have overlooked important references of which they are not aware, and, furthermore, to have added to the burden of the reader. This book has a definite value as a reference and source material, and while it does not give to-the-point information which the American surgeon is accustomed to find in his familiar texts, it certainly fills in many of the hiatuses in our surgical texts which sometimes cause our own works to be clipped and foreshortened. The book is well printed, its excellent format makes for easy and efficient reading, and it is fairly well indexed. Unfortunately, like many books of foreign origin, it is poorly bound and will not withstand rough or heavy use. JOHN MARTIN.

THE authors, a gynecologist and an endocrinologist, have summarized in *Psychosomatic Gynecology*[3] a great deal of the extensive literature concerning the relation of emotional factors to obstetric and gynecologic problems. To this they have added the results of their own observations to produce an exceedingly interesting volume.

The text is divided into five parts. Part I considers the psychosomatic aspects of the fetus and infant. One chapter of Part II which deals with the psychosomatic aspects of the mother during pregnancy has been written by Grantly Dick Read. It is a discussion of the psychological preparation of the patient during the antenatal period and natural childbirth. Part III takes up the psychosomatic aspects of neuroendocrinology, particularly as they relate to disturbances of the menstrual cycle. Part IV, common psychosomatic problems, presents not only those disturbances commonly considered as having a possible psychogenic background, but also a number of gynecologic problems which are not ordinarily associated with emotional disturbance. Among the latter are sterility, retroversion of the uterus, uterine prolapse, cystocele, stress incontinence, uterine myomas and neoplasms. Part V discusses methods of diagnosis and treatment. It is a detailed discussion of psychogenic therapy, including the technique of hypnoanalysis.

The book unquestionably answers a serious need for it brings together in one volume the literature on a frequently discussed and most important subject. There is no doubt that the gynecologist and obstetrician who read it will gain a more comprehensive concept of the role of the emotions in gynecologic complaints. However, many gynecologists and obstetricians, less "dynamically oriented" than the authors, are apt not to share their enthusiasm in attributing the causes of some entities commonly considered of organic origin to psychodynamic factors. Scientifically trained and analytically minded skeptics may have difficulty in accepting a considerable part of the evidence used to prove the

[1]HEART DISEASE. By Paul Dudley White, M.D. 4th ed. New York: The Macmillan Co., 1951.

[2]TRAITÉ DE THÉRAPEUTIQUE CHIRURGICALE (A Treatise on Surgical Therapy). By P. Bertrand, and J. Creyssel. Vols. 1 and 2. Paris: G. Doin & Cie, 1951.

[3]PSYCHOSOMATIC GYNECOLOGY; INCLUDING PROBLEMS OF OBSTETRICAL CARE. By William S. Kroger, M.D., and S. Charles Freed, M.D. Philadelphia and London: W. B. Saunders Co., 1951.

role of emotional instability in organic disease. They must, however, agree that the text justifiably emphasizes the importance of emotional problems in genital dysfunctions. JOHN W. HUFFMAN.

THE overwhelming wealth of material and the splendid documentation by almost 400 illustrations makes it impossible for any reviewer to do justice to *Die gesunde und kranke Wirbelsaeule in Roentgenbild und Klinik; Pathologisch-anatomische Untersuchungen*[1] without studying it closely from cover to cover. In 9 chapters the authors discussed practically all conceivable situations involving the human spine. The greatest value of this work lies in the meticulous juxtaposition of pathological specimens with their respective roentgenological corollaries.

The first chapter, dealing with normal structure and growth of the spine, clear and instructive as it is, is overshadowed by the following which covers the congenital anomalies. In the chapter on degenerative changes, those of the intervertebral disc are given particularly extensive study as one would expect from the discoverer of "Schmorl's nodes." It is difficult to select one particular chapter for its instructional value but we would name those on the morbid changes of the intervertebral disc, and that on the disease of the spinal columns as truly outstanding. These are in every respect complete and comprehensive, they are admirably presented and profusely documented by most excellent illustrations. The review of an incredibly voluminous literature reflects the intensive labor which the authors have devoted to their task.

This work is a fitting monument to the greatness of Georg Schmorl, who, with his enormous experience has laid the foundation for the pathology of the spine and had based the first edition of this work upon his vast knowledge of the subject. Herbert Junghanns is another recognized authority in roentgen diagnosis. He has in this second edition carried on Schmorl's work after the latter's untimely death in 1932. It is a classic in every sense—for its wealth of material, for its clearness in presentation, and for the high artistic standard of its illustrations. A. STEINDLER.

THE author, an associate professor of ophthalmology at Temple University School of Medicine, presents *Textbook of Refraction*[2] as an amplification of the outlines and notes used in the classroom, with pertinent references appended to each chapter. The text presupposes a fair knowledge of anatomy and physiology of the eye and of the nervous system and of geometric and physiologic optics.

The volume includes chapters on vision, ocular reflexes, accommodation stimulus, response mechanism, anomalies and variations of ocular accommodation, emmetropia and ametropia, hyperopia, myopia, astigmia, presbyopia, and aphakia. Isometropia, anisometropia and aniseikonia, amblyopia, reading difficulties, visual screening, illumination and photophobia, binocular co-ordination, physiology and anatomy of the ocular muscles, ocular muscle anomalies, methods of refraction, including static and dynamic skiametry, diagnosis and correction of heterophoria, diagnosis and correction of heterophoria are all considered. The last chapter gives in great detail a routine to follow while making an eye examination. BEULAH CUSHMAN.

WE are pleased to find so soon another installment of the exceptional work *Lehrbuch der Roentgendiagnostik*[3] before us for review. There will be 10 such parts in the complete work. We have seen the 4 on the skeleton; 2 will be devoted to the thorax, another 2 to the digestive organs, and a final 2 to the subjects of gynecology and obstetrics, urology, and some miscellaneous subjects to make this publication the most inclusive and complete reference work on radiology in existence.

This particular part (5) deals with the thorax. It is difficult to find any phase of intrathoracic pathologic variation from the normal not included in these pages. The introductory section deals with the normal thorax and its contents. The remainder of the more than 400 pages of this section concerns the pathologic trachea, bronchi and lungs; pleural lesions evidently are to be discussed in part 6, along with the cardiovascular system. Exceptionally detailed consideration is given to pulmonary tuberculosis and the various kinds of inhalation diseases and the various types of pneumonia. The reader will find the text most comprehensive. As usual, the illustrations are superb. The bibliography is full, including many references to American and British literature. Any deficiencies in this regard will be taken care of in the English translation already being published. JAMES T. CASE.

THE new seventh edition of *A Textbook of Clinical Neurology*[4] by Israel S. Wechsler, is essentially, as were its predecessors, a textbook of clinical neurology that should serve as an excellent reference for the medical student and general practitioner.

This completely re-edited edition contains a well written section on psychological diagnosis under the section on "Method of Examination" and contains 32 pages at the end of the book devoted to an introduction to the history of neurology.

[1] DIE GESUNDE UND KRANKE WIRBELSAEULE IN ROENTGENBILD UND KLINIK; PATHOLOGISCH-ANATOMISCHE UNTERSUCHUNGEN. By Dr. Med. Georg Schmorl and Herbert Junghanns. 2nd enl. ed. Stuttgart: Georg Thieme, 1951.

[2] TEXTBOOK OF REFRACTION. By Edwin Forbes Tait, M.D., Ph.D. Philadelphia: W. B. Saunders Co., 1951.

[3] LEHRBUCH DER ROENTGENDIAGNOSTIK. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. No. 5, Inner Organ, Stuttgart: Georg Thieme, 1951.

[4] A TEXTBOOK OF CLINICAL NEUROLOGY; WITH AN INTRODUCTION TO THE HISTORY OF NEUROLOGY. By Israel S. Wechsler, M.D. 7th ed. Philadelphia, London: W. B. Saunders Co., 1952.

The more notable changes in this edition include the treatment of the meningitides. It is particularly interesting to note that the author advocates the use of intrathecal penicillin in the treatment of pneumococcic meningitis, in keeping with the writings of H. Cairns and in spite of the contraindications for intrathecal therapy as noted by A. L. Hoyne. He also advocates the continued treatment of tuberculous meningitis with streptomycin for months in spite of apparent remissions. The author warns the reader of the dangers of the treatment of syphilis of the nervous system with malaria, suggesting that severe anemia, cardiac failure, pyelitis, jaundice, or other infectious processes indicate that termination of the malarial treatment is in order.

The average medical student may be somewhat overwhelmed by the number of syndromes mentioned throughout the text such as: the syndrome of Gerhardt, syndrome of Vernet, syndrome of Villaret and Collet, and the syndrome of Schmidt. One would scarcely expect him to remember terms such as: Minor's sign or the sign of Neri.

The text is well written and easy to read; the sentences are relatively short and uncomplicated. Excellent references may be found at the end of each chapter and the majority of these references are to the English literature.

The sentence on page 21, "All the Greeks through the Alexandrian and Roman periods down to Celsus, Galen, and Aretaeus, confused tendons with nerves" must bring a smile to those surgeons who are called upon to repair or correct secondarily lesions that have been too hastily repaired primarily.

JOSEPH TARKINGTON.

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# BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

CURRENT THERAPY 1952; LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN. Edited by Howard F. Conn, M.D., and other consulting editors. Philadelphia, London: W. B. Saunders Co., 1952.

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# CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

ALTON OCHSNER, New Orleans, *President*
HAROLD L. FOSS, Danville, Pennsylvania, *President-Elect*

## PRELIMINARY PLANS FOR 38TH CLINICAL CONGRESS, THE WALDORF-ASTORIA, NEW YORK SEPTEMBER 22 TO 26, 1952

THE program of this year's Clinical Congress will follow a general plan similar to that of recent Congresses. Attention is called, however, to the increased number of sessions devoted to programs for the surgical specialties.

In addition to the customary three day period of special programs for ophthalmology and for otolaryngology, the College's Advisory Council for Gynecology and Obstetrics has arranged for this Congress a three day separate program of panel discussion sessions. Also, the Surgical Forum Committee will provide a separate forum session for each of those surgical specialties submitting a sufficient number of reports of research work.

The general scientific sessions and the programs planned for the different surgical specialties are outlined below. The detailed program will be announced later. Sessions and exhibits will be centered in the one major hotel, The Waldorf-Astoria, with some meetings at the Hotel Belmont-Plaza across the street and The Biltmore, which is also nearby.

Subjects of the programs planned for the general scientific sessions and for the different surgical specialties are as follows:

### EVENING SESSIONS

Cytologic and Biopsy Diagnosis of Cancer.
Evaluation of Cancer Diagnostic Tests.
Cancer of the Lung.
Trauma Oration.
Medical Management of Thromboembolic Disease, with an Evaluation of the Newer Anticoagulants.
The Management of Thromboembolic Disease in Surgical Patients.
Laryngeal Sequelae of Intratracheal Anesthesia.
Conservative Surgical Treatment of Endometriosis.
Evaluation of Liver Function Tests.

### PANEL DISCUSSION SESSIONS IN GENERAL SURGERY

Choice of Operation for Cancer of the Rectum.
Blood, Plasma, and Plasma Expanders.
Gallbladder Disease.
Carcinoma of the Stomach.
Pancreatic Disease.
Postphlebitic Syndrome.
Current Practice in Management of Problems Concerning Water, Electrolyte, and Protein Balance in Surgical Patients.

### PANEL DISCUSSIONS FOR SURGICAL SPECIALTIES

*Neurologic Surgery*

The Treatment of Intracranial Glioblastomas.
The Diagnosis and Results of Treatment of Herniated Nucleus Pulposus in the Cervical Spinal Canal.

*Orthopedic Surgery*

Indications and Technique for Internal Fixation, Including Use of the Intramedullary Nail, of Fractures of the Shaft of the Femur.
Indications and Technique for Internal Fixation, Including Use of the Intramedullary Nail, of Fractures of the Tibia.

*Plastic Surgery*

The Treatment of Compound Injuries Complicated by Extensive Loss of Covering Tissue.
The Replacement of Extensive Scars About Lower Leg, Ankle, and Foot with Sliding Flaps and with Cross-leg Flaps.

*Thoracic Surgery*

The Problem of Cardiac Arrest; Its Prevention and Treatment.
Recent Developments in the Surgical Treatment of Pulmonary Tuberculosis.

*Urology*

Management of Surgical Injuries Occurring in the Urinary Tract.
Management of the Congenital Anomalies of the Urinary Tract.

### PANEL DISCUSSIONS FOR GYNECOLOGY AND OBSTETRICS

Pain in the Right Lower Quadrant of the Female Abdomen.
Urological Survey Before and After Gynecologic Surgery.
Management of the Rh Negative Patient.
The Present Status of the Vaginal Smear in Diagnosis of Malignancy.
Diagnostic Procedure and Treatment of Nonmalignant Lesions Causing Bleeding.

### OPHTHALMOLOGY

Program will include the following subjects:

Problems Concerned with the Extraction of Complicated Cataracts (panel discussion).
Surgical Correction of Motor Anomalies Involving the Extraocular Muscles (symposium).
Orbital Implants (panel discussion).
Causes of Failures in Ocular Surgical Procedures (symposium).
Fallacies in Refraction by Use of Mechanical Refractors (panel discussion).
Sympathetic Ophthalmia.
Atomic Eye Injuries.
Management of Intraocular Foreign Bodies.
Treatment of Eye Burns.

### OTOLARYNGOLOGY

Program will include the following subjects:

Nasopharyngeal Fibromas (panel discussion).
Teratological Lesions of the Head and Neck.
Blood Substitutes.
Mycotic Infections.
Treatment of Hemangiomas.
Modified Radical Mastoidectomy.
Infectious Mononucleosis.
Symposium on Re-evaluation of Antibiotics.
Respiratory Obstructions in Infants, Including Atelectasis in the Newborn.
Differential Diagnosis of Wheezing Respirations.
Management of Respiratory Difficulty in Bulbar Poliomyelitis.
Operating Room Emergencies (symposium).

### SPECIAL SYMPOSIA

Important problems in the fields of trauma, cancer, and graduate training.

### FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

Research papers of special importance to surgeons.

### POSTGRADUATE COURSES

Gynecology and Obstetrics.
Management of Fractures.
Nonmalignant Diseases of the Gastrointestinal Tract.
Nutrition and Preoperative and Postoperative Care of the Surgical Patient.
Surgical Aspects of Pulmonary Disease.
Trauma of the Skull and Spine.
Vascular Diseases.

The programs of Ciné clinics, medical motion pictures, and color television will include surgical procedures of current interest.

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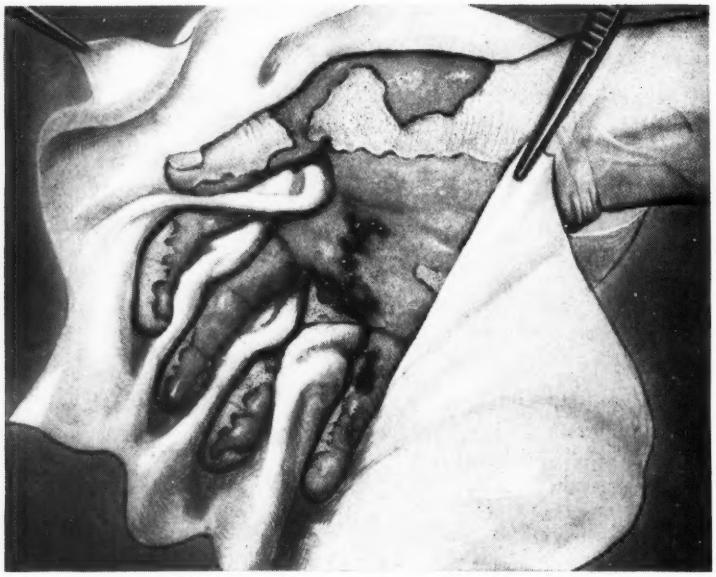
# SURGERY Gynecology and Obstetrics

## With International Abstracts of Surgery

VOLUME 94 June, 1952 NUMBER 6



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2. *Prevents infection.* It suppresses growth of many organisms which might be present in the wound or later contaminate it.
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5. *Non-toxic.* Reactions to Aureomycin Dressing so far have not been observed.

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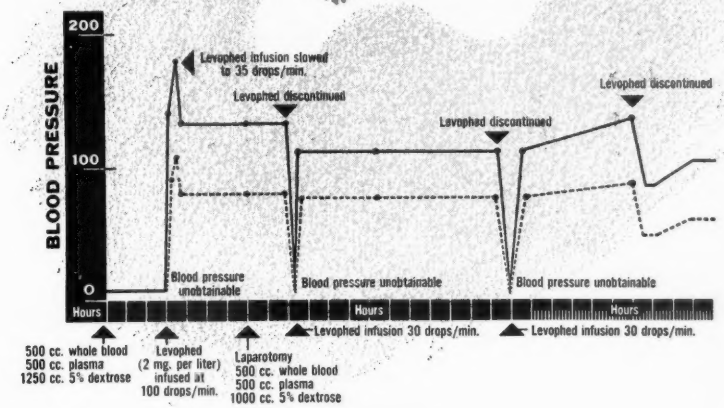


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1. Barnett, S.E.: Eye, Ear, Nose & Throat Monthly *39*:19,

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